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(54) Azetidines

Azetidine

Azétidines

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(56) References cited:

EP-A- 0 512 901	EP-A- 0 673 928
WO-A-95/12577	WO-A-96/05193

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Description

[0001] This invention relates to therapeutic agents of the glutarimide family. More particularly, this invention relates to azetidinylalkylglutarimide derivatives and to processes for the preparation of, intermediates used in the preparation of, compositions containing and uses of, such compounds.

5 [0002] International Patent Publication Number WO 96/05193 discloses various (azetidin-1-ylalkyl) lactams as tachykinin antagonists.

[0003] International Patent Publication Number WO 95/12577 discloses a class of 4-piperidinyl substituted lactams as tachykinin antagonists.

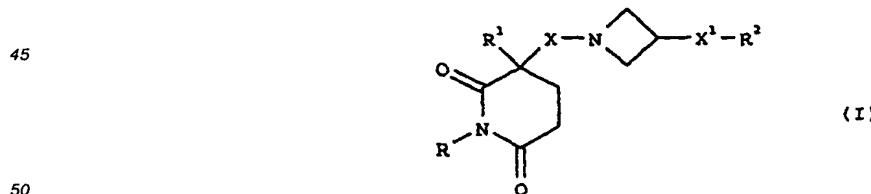
10 [0004] European Patent 0673 928B1 teaches a class of N(3,4-dichlorophenyl-propyl)piperidine derivatives as selective NK₃ receptor antagonists.

[0005] European Patent 0512 901B1 discloses a range of animated polycyclic compounds which encompass a class of piperidine derivatives.

15 [0006] The present azetidinylalkylglutarimides are antagonists of tachykinins, including neurokinin A (NKA), neurokinin B (NKB) and Substance P, acting at the human neurokinin-1 (NK₁), neurokinin-2 (NK₂) or neurokinin-3 (NK₃) receptor, or a combination of two or more thereof. They are therefore useful for preventing or treating an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a disease caused by *Helicobacter pylori* or other urease positive Gram negative bacteria, a urogenital tract disorder such as incontinence, hyperreflexia, impotence or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis, atopic dermatitis, urticaria, eczematoid dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a vasospastic disease such as angina or Reynaud's disease, a proliferative disorder such as cancer or a disorder involving fibroblast proliferation, a fibrosing or collagen disease such as scleroderma or eosinophilic fascioliasis, reflux sympathetic dystrophy such as shoulder/hand syndrome, an addiction disorder such as alcoholism, a stress-related somatic disorder, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, a neuropathological disorder such as Alzheimer's disease or multiple sclerosis, a disorder related to immune enhancement or suppression such as systemic lupus erythematosus, a rheumatic disease such as fibrositis, emesis, cough, acute or chronic pain, migraine, an ophthalmic disease such as proliferative retinopathy, or a viral disease such as influenza or a cold.

20 [0007] The present derivatives are particularly potent and selective antagonists of tachykinins, including NKA, NKB and Substance P, acting at the human NK₁, NK₂ and NK₃ receptors or combinations of two or more thereof. They are particularly useful for treating or preventing an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a urogenital tract disorder such as incontinence or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.

25 [0008] The present invention provides compounds of the formula (I):-



and the pharmaceutically acceptable salts thereof, wherein

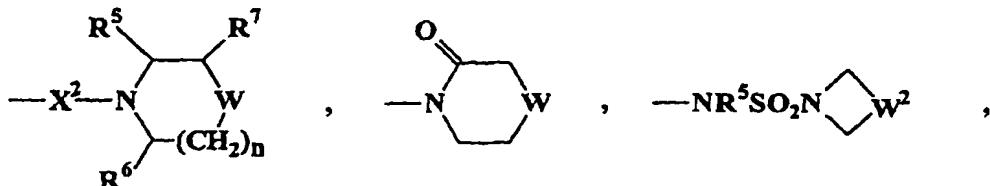
55 R is C₃-C₇ cycloalkyl, aryl or C₁-C₆ alkyl, said C₁-C₆ alkyl being optionally substituted by fluoro, -COOH, -COO (C₁-C₄) alkyl, C₃-C₇ cycloalkyl, adamantyl, aryl or het¹, and said C₃-C₇ cycloalkyl being optionally substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, C₃-C₇ cycloalkyl, C₁-C₄ alkoxy, hydroxy, fluoro, fluoro (C₁-C₄) alkyl and fluoro(C₁-C₄)alkoxy;

R¹ is phenyl, benzyl, naphthyl, thiaryl, benzothiaryl or indolyl, each optionally substituted by 1 or 2 substituents each

independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo and trifluoromethyl;
 R² is -CO₂H, -CONR³R⁴, -CONR⁵(C₃-C₇ cycloalkyl), -NR⁵(C₂-C₅ alkanoyl), -NR³R⁴, -NR⁵CONR⁵R⁶, (C₃-C₇ cycloalkyl-C₁-C₄ alkyl)R⁵N-, (C₃-C₇ cycloalkyl-C₁-C₄ alkyl)₂N-, -NR⁵COCF₃, -NR⁵SO₂CF₃, -NR⁵(SO₂C₁-C₄ alkyl), -NR⁵SO₂NR⁵R⁶, -NR⁵(SO₂ aryl), -N(aryl)(SO₂C₁-C₄ alkyl), -OR⁵, -O(C₃-C₇ cycloalkyl), -SO₂NR⁵R⁶, het³ or a group of the formula:-

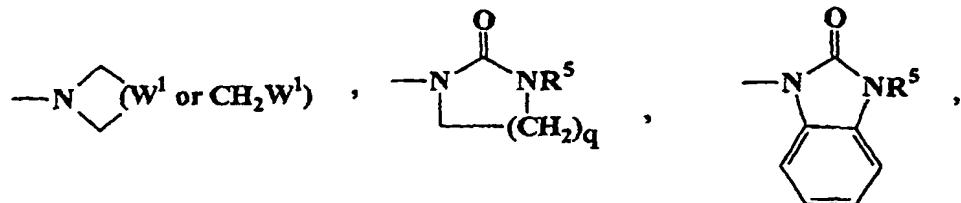
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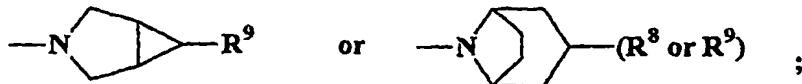
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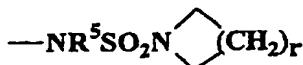
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R³ and R⁴ are each independently selected from H and C₁-C₄ alkyl optionally substituted by hydroxy, C₁-C₄ alkoxy, -S(O)_p(C₁-C₄ alkyl), amino, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or het²;
 R⁵ and R⁶ are each independently selected from H, C₁-C₄ alkyl and C₃-C₇ cycloalkyl-C₁-C₄ alkyl, said C₁-C₄ alkyl and C₃-C₇ cycloalkyl-C₁-C₄ alkyl being optionally substituted by fluoro;
 R⁷ is H, C₁-C₄ alkyl, hydroxy, fluoro(C₁-C₄)alkyl or phenyl, said phenyl being optionally substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, fluoro(C₁-C₄)alkyl, halo, C₁-C₄ alkoxy and fluoro(C₁-C₄)alkoxy;
 R⁸ is H, fluoro, hydroxy, C₁-C₄ alkoxy, C₂-C₅ alkanoyl or C₂-C₅ alkanoyloxy;
 R⁹ is -NR⁵R⁶, -NR⁵COR⁵, -NR⁵SO₂CF₃, -NR⁵(SO₂C₁-C₄ alkyl), -NR⁵SO₂NR⁵R⁶, -NR⁵COO(C₁-C₄ alkyl), -NR⁵CONR⁵R⁶, -NR⁵(SO₂morpholino), -NR⁵(SO₂ aryl), -N(aryl)(SO₂C₁-C₄ alkyl) or a group of the formula:-

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X is C₁-C₄ alkylene;
 X¹ is a direct link or C₁-C₆ alkylene;
 X² is a direct link, CO, SO₂ or NR⁵CO where the carbonyl is attached to the ring nitrogen atom;
 W is methylene, CO, CH(OH), C(OH)₂, CH(C₁-C₄ alkoxy), CHCO₂H, CHCO₂(C₁-C₄ alkyl), CHCONR⁵R⁶, CHF, CF₂, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino), CH(benzoxazol-2-yl), CHR⁹, O, S(O)_p, NR⁵, N(C₃-C₇ cycloalkyl), NSO₂(C₁-C₄ alkyl), NSO₂NR⁵R⁶, NSO₂CF₃, NSO₂(morpholino), NSO₂(aryl),



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NCONR⁵R⁶, NCOR⁵, NCO(aryl) or NCO₂(C₁-C₄ alkyl);
 W¹ is methylene, CO, CH(OH), C(OH)₂, CH(C₁-C₄ alkoxy), CHCO₂H, CHCO₂(C₁-C₄ alkyl), CHCONR⁵R⁶, CHF, CF₂, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino) or CHR⁹;

W² is W¹, -CH₂W¹-, -CH₂WCH₂- or -CH₂CH₂WCH₂-,
 n is 1 or 2 when W is other than methylene and is 0, 1 or 2 when W is methylene;
 p is 0, 1 or 2;
 q is 1 or 2;
 r is 1, 2, 3 or 4;

"aryl", used in the definition of R, R², R⁹ and W, means naphthyl or phenyl, each optionally substituted by C₁-C₄ alkyl, halo, -OR⁵, fluoro(C₁-C₄)alkyl, C₂-C₅ alkanoyl, -CONR⁵R⁶, -SO₂NR⁵R⁶ or phenyl;
 "het¹", used in the definition of R, means thienyl or a 5- or 6-membered ring heteroaryl group containing either 1 or 2 nitrogen heteroatoms or one nitrogen heteroatom and one oxygen or sulphur heteroatom, each optionally substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, fluoro(C₁-C₄ alkyl) and fluoro(C₁-C₄ alkoxy);

"het²", used in the definitions of R³ and R⁴, means a 4-to 7-membered ring, non-aromatic, heterocyclic group containing 1 or 2 heteroatoms each independently selected from nitrogen, oxygen and S(O)_p, said group being optionally C-substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and fluoro(C₁-C₄)alkyl, and said ring nitrogen heteroatom optionally bearing a H, C₁-C₄ alkyl, C₂-C₅ alkanoyl, -CONR⁵R⁶ or -SO₂NR⁵R⁶ substituent;

25 and "het³", used in the definition of R², means an optionally benzo-fused, N-linked, 5-membered ring heteroaryl group containing from 1 to 4 nitrogen heteroatoms, which het³ is optionally substituted, including in the benzo-fused portion, by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, fluoro and fluoro(C₁-C₄)alkyl.

[0009] In the above definitions, the term "halo" means fluoro, chloro, bromo or iodo and alkyl, alkylene and alkoxy groups containing three or more carbon atoms and alkanoyl groups containing four or more carbon atoms can be straight- or branched-chain.

[0010] Preferably R is aryl, optionally substituted C₃-C₇ cycloalkyl, or is C₁-C₆ alkyl substituted by aryl or optionally substituted C₃-C₇ cycloalkyl.

[0011] More preferably, R is optionally substituted C₃-C₇ cycloalkyl or C₁-C₆ alkyl substituted by optionally substituted C₃-C₇ cycloalkyl.

35 [0012] Most preferably R is 2-cyclopropylethyl, cyclohexyl, 4,4-difluorocyclohexyl, cyclohexylmethyl or cyclopropylmethyl.

[0013] Preferably, R¹ is phenyl optionally substituted by 1 or 2 halo substituents.

[0014] More preferably, R¹ is phenyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and chloro.

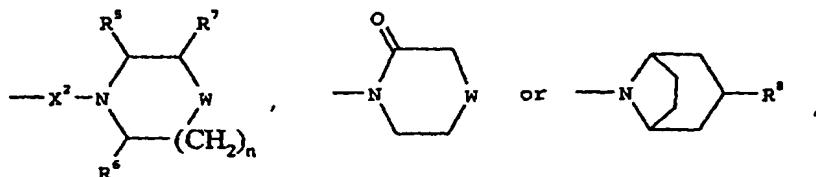
40 [0015] Yet more preferably, R¹ is phenyl, 3,4-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl or 3,4-dichlorophenyl.

[0016] Most preferably, R¹ is 3,4-dichlorophenyl.

[0017] Preferably, R² is -CONR³R⁴, -CONR⁵(C₃-C₇ cycloalkyl), -NR³R⁴, het³ or a group of the formula:-

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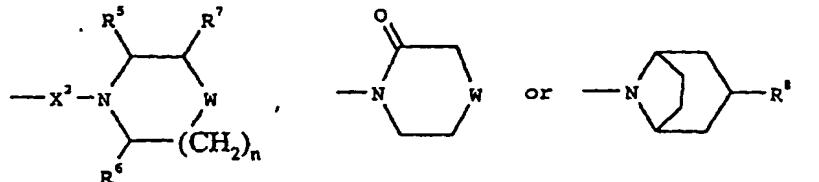
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55 where R³ and R⁴ are each independently selected from C₁-C₄ alkyl and C₁-C₄ alkyl substituted by hydroxy or C₁-C₄ alkoxy, R⁵ and R⁶ are each independently selected from H, C₁-C₄ alkyl optionally substituted by fluoro and C₃-C₇ cycloalkyl-C₁-C₄ alkyl, R⁷ is H, hydroxy or phenyl, R⁸ is hydroxy or C₂-C₅ alkanoyloxy, W is methylene, CH(OH), CHF, CO, CH(C₁-C₄ alkoxy), CHCO₂H, CHCO₂(C₁-C₄ alkyl), CH(benzoxazol-2-yl), CHNR⁵R⁶, CHNR⁵COR⁵, CHNR⁵

($\text{SO}_2\text{C}_1\text{-C}_4$ alkyl), $\text{CHNR}^5\text{COO}(\text{C}_1\text{-C}_4$ alkyl), O, S(O)_p , $\text{NR}^5\text{NSO}_2(\text{C}_1\text{-C}_4$ alkyl), $\text{NSO}_2\text{NR}^5\text{R}^6$, NSO_2 (morpholino), NSO_2 (piperidino), NCONR^5R^6 , NCOR^5 , NCO(aryl) or $\text{NCO}_2(\text{C}_1\text{-C}_4$ alkyl), n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, 1 or 2.

5 [0018] More preferably, R^2 is $-\text{CONR}^3\text{R}^4$, $-\text{CONR}^5(\text{C}_3\text{-C}_7$ cycloalkyl), $-\text{NR}^3\text{R}^4$, a N-linked, 5-membered ring heteroaryl group containing 1 or 2 nitrogen heteroatoms, or a group of the formula:-



where R^3 and R^4 are each independently selected from methyl and $\text{C}_1\text{-C}_4$ alkyl substituted by hydroxy or methoxy, R^5 and R^6 are each independently selected from H, methyl, trifluoromethyl and cyclopropylmethyl, R^7 is H, hydroxy or phenyl, R^8 is hydroxy or acetoxy, W is methylene, CH(OH) , CHOCH_3 , CHF , CO, $\text{CHOCH}_2\text{CH}_3$, $\text{CHO}(\text{CH}_2)_2\text{CH}_3$, $\text{CHOC}(\text{CH}_3)_3$, CHCO_2H , CHCO_2CH_3 , $\text{CHCO}_2\text{CH}_2\text{CH}_3$, $\text{CH}(\text{benzoxazol-2-yl})$, CHNH_2 , CHNHCH_2 (cyclopropyl), CHNHCOCH_3 , $\text{CHNSO}_2\text{CH}_3$, $\text{CHNHCO}_2\text{C}(\text{CH}_3)_3$, O, S(O)_p , NH, NCH_3 , NCH_2 (cyclopropyl), NSO_2CH_3 , NSO_2NH_2 , $\text{NSO}_2\text{NHCH}_3$, $\text{NSO}_2\text{N}(\text{CH}_3)_2$, NSO_2 (morpholino), NSO_2 (piperidino), NCONH_2 , NCONHCH_3 , NCOCH_3 , NCOCF_3 , NCO(phenyl) or $\text{NCO}_2\text{C}(\text{CH}_3)_3$, n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, 1 or 2.

20 [0019] Yet more preferably, R^2 is N-(2-methoxyethyl)-N-methylcarbamoyl, N-cyclohexylcarbamoyl, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxy-2-methylpropyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, imidazol-1-yl, 3-hydroxypyrrrolidin-1-yl, piperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 3-hydroxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, 4-methoxypiperidin-1-yl, 4-ethoxypiperidin-1-yl, 4-(n-propoxy)piperidin-1-yl, 4-(t-butoxy)piperidin-1-yl, 4-carboxypropiperidin-1-yl, 4-methoxycarbonylpiperidin-1-yl, 4-ethoxycarbonylpiperidin-1-yl, 4-(benzoxazol-2-yl)piperidin-1-yl, 4-aminopiperidin-1-yl, 4-cyclopropylmethylaminopiperidin-1-yl, 4-acetamidopiperidin-1-yl, 4-methanesulphonamidopiperidin-1-yl, 4-(t-butoxycarbonylamino)piperidin-1-yl, morpholino, 2-phenylmorpholino, homomorpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-cyclopropylmethylpiperazin-1-yl, 4-methanesulphonylpiperazin-1-yl, 4-aminosulphonylpiperazin-1-yl, 4-methylaminosulphonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl, 4-carbamoylpiperazin-1-yl, 4-N-methylcarbamoylpiperazin-1-yl, 4-acetyl piperazin-1-yl, 4-trifluoroacetyl piperazin-1-yl, 4-benzoylpiperazin-1-yl, 4-(t-butoxycarbonyl)piperazin-1-yl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, 3-oxomorpholino, 3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl, 3-acetoxy-8-azabicyclo[3.2.1]oct-8-yl, 4-fluoropiperidin-1-yl or 4-oxopiperidin-1-yl.

25 [0020] Most preferably, R^2 is 4-aminopiperidin-1-yl, 4-carboxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 1-oxothiomorpholino, 4-aminosulphonylpiperazin-1-yl, 4-methanesulphonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl or 4-oxopiperidin-1-yl.

30 [0021] Preferably, X is ethylene or propylene.

[0022] Preferably, X^1 is a direct link.

[0023] Preferably, X^2 is a direct link.

35 [0024] The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

40 [0025] Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

45 [0026] Suitable base salts are formed from bases which form non-toxic salts and examples are the aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

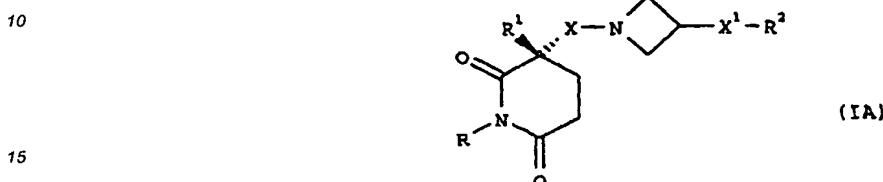
[0027] For a review on suitable salts see Berge *et al*, *J. Pharm. Sci.*, **66**, 1-19 (1977).

50 [0028] A compound of the formula (I) may contain one or more asymmetric carbon atoms and may therefore exist in two or more stereoisomeric forms. The present invention includes the individual stereoisomers of the compounds of the formula (I) and mixtures thereof.

55 [0029] Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative

thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base.

5 [0030] The preferred compounds of the formula (I) and salts thereof have the stereochemistry shown below in formula (IA) at the position of attachment of the X and R¹ groups to the glutarimide ring:



Preferred examples of a compound of formula (I) are those wherein:

20 (i) R is cyclohexylmethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is morpholino;

(ii) R is cyclohexylmethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is 4-aminosulphonyl-piperazin-1-yl;

25 (iii) R is cyclopropylmethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is 4-morpholinosulphonylpiperazin-1-yl;

(iv) R is cyclopropylmethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is 4-aminosulphonyl-piperazin-1-yl;

30 (v) R is cyclopropylethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is 4-dimethylamino-sulphonylpiperazin-1-yl;

(vi) R is cyclopropylethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is 4-piperidinosulphonylpiperazin-1-yl;

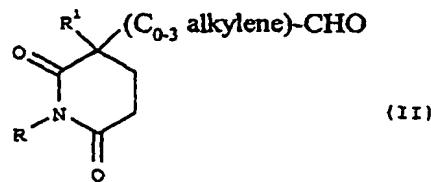
35 (vii) R is cyclopropylethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is 4-aminosulphonyl-piperazin-1-yl; or

40 (viii) R is cyclopropylethyl, R¹ is 3,4-dichlorophenyl, X is ethylene, X¹ is a direct link and R² is morpholino;

45 or any such compound with the stereochemistry shown above for the compound of the formula (IA) at the position of attachment of the X and R¹ groups to the glutarimide ring, or a pharmaceutically acceptable salt of any thereof.

[0031] The compounds of the formula (I) provided by the invention can be prepared by the following methods:-

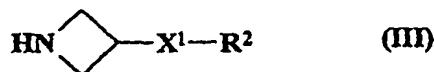
50 1) The compounds of the formula (I) where X is (C₀-C₃ alkylene)CH₂-, the methylene group of which is attached to the azetidine nitrogen atom, and R, R¹, R² and X¹ are as previously defined for a compound of the formula (I) can be prepared by reductive amination using as starting materials a compound of the formula:-



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where R and R¹ are as previously defined for a compound of the formula (I), and a compound of the formula:-

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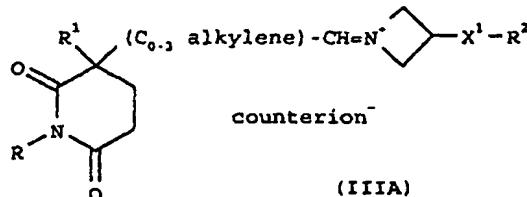


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, or an acid addition salt thereof, where R² and X¹ are as previously defined for a compound of the formula (I). The reaction is preferably carried out in the presence of a suitable acid, e.g. acetic acid.

The reaction proceeds via the initial formation of an intermediate iminium species of the formula:

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where the counterion depends on the acid species present in the reaction, and can for example be OH or CH₃CO₂. The species of formula (IIIA) may be stable and isolatable. The reaction is preferably carried out without isolation of the intermediate of the formula (IIIA) in which case it is reduced in situ to provide a compound of formula (I).

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In a typical procedure, an aldehyde of the formula (II) is first reacted with an azetidine of the formula (III) in a suitable solvent, e.g. tetrahydrofuran, and the mixture then treated with a suitable reducing agent, e.g. sodium triacetoxyborohydride or sodium cyanoborohydride, in the presence of a suitable acid, e.g. acetic acid, to give the required product. If an acid addition salt of an azetidine of the formula (III) is used as a starting material, a suitable acid acceptor, e.g. triethylamine, can be added prior to the addition of the reducing agent.

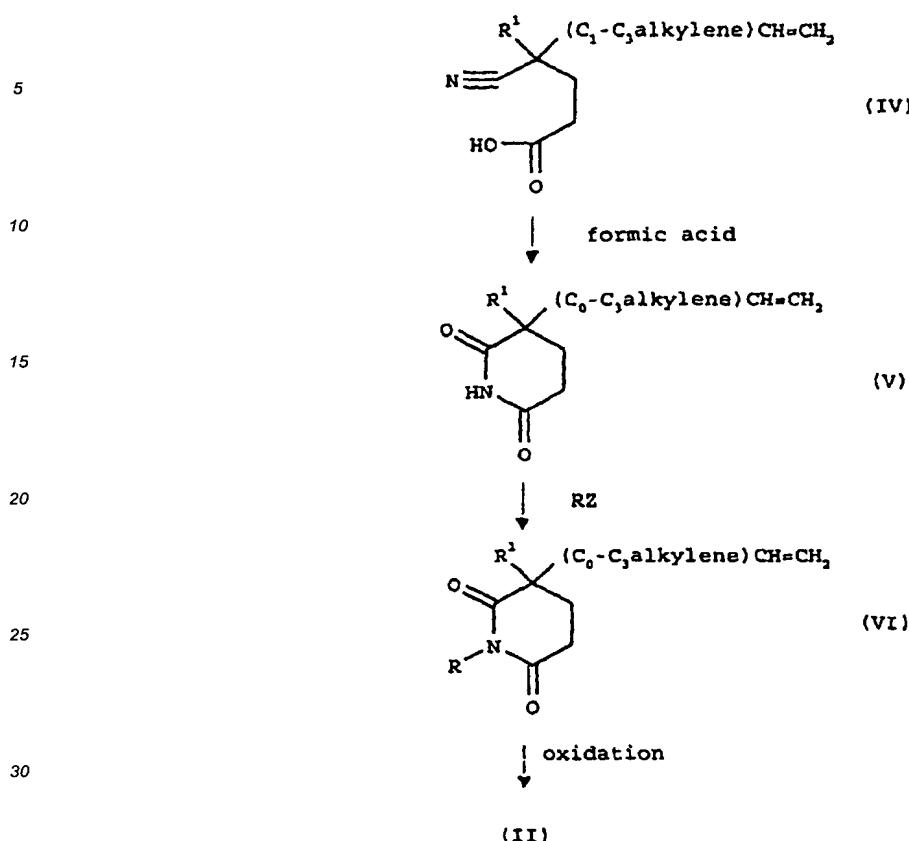
The reaction is typically carried out at room temperature.

The starting aldehydes of the formula (II) can be prepared by the method shown in the Scheme below:-

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35 where R and R¹ are as previously defined for a compound of the formula (I) and Z is a suitable leaving group, e.g. chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethylsulphonyloxy.

Starting materials of formula (IV) where R¹ is as defined for compounds of formula (I) can be made by conventional methods such as by adaptation of the methods described in the Experimental section.

40 Glutarimides of formula (V) where R¹ is as defined for compounds of formula (I) can be made by reaction of compounds of formula (IV) with formic acid. The reaction is preferably carried out in the presence of an aqueous acid such as hydrochloric acid, and a polar solvent such as N,N-dimethylformamide, preferably at elevated temperatures.

45 N-Substituted glutarimides of formula (VI) can be made from compounds of formula (V) by reaction with reagents RZ, where R is as defined for compounds of formula (I), and Z is as defined above. Preferably, Z is bromo. The reaction is preferably carried out in the presence of a base, such as sodium hydride, in a polar solvent such as N,N-dimethylformamide, at elevated temperatures.

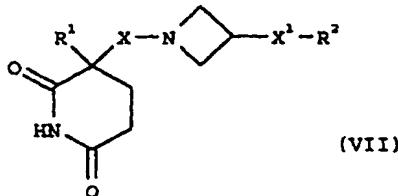
The alkene moiety of the compounds of formula (VI), where R and R¹ are as previously defined, can then be oxidised, for example by ozonolysis using a dimethyl sulphide work-up, to give aldehydes (III).

50 The reagents of the formula RZ can be prepared by conventional methods such as by adaptation of the preparations described hereafter and in "Advanced Organic Chemistry" by J.March (3rd edn., Wiley-Interscience) and the references therein.

The starting azetidines of the formula (III) may be prepared by conventional methods.

55 2) All the compounds of the formula (I), where X, X¹, R, R¹ and R² are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (VII):-

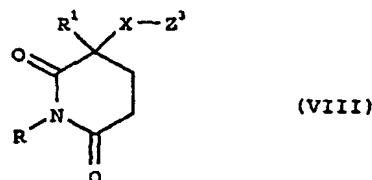
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10 where X, X¹, R¹ and R² are as previously defined for a compound of the formula (I), with a compound of the formula RZ, where R and Z are as previously defined and the reactions are carried out in a similar manner to those described earlier for the transformation (V) to (VI).

15 The reagents of the formula RZ can be prepared by conventional methods such as by adaptation of the preparations described hereafter and in "Advanced Organic Chemistry" by J. March (3rd edn., Wiley-Interscience) and the references therein.

20 3) All the compounds of the formula (I) where X, X¹, R, R¹ and R² are as previously defined for a compound of the formula (I) can be prepared by reaction of a compound of the formula (VIII):-



30 where X, R and R¹ are as previously defined for a compound of the formula (I) and Z³ is a suitable leaving group, e.g. chloro, bromo, iodo, methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy, with a compound of the formula:-

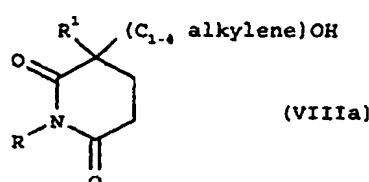


40 where R² and X¹ is as previously defined for a compound of the formula (I).

45 In a typical procedure, a compound of the formula (VIII) where Z³ is preferably methanesulphonyloxy, is reacted with a compound of the formula (III) in the presence of a suitable acid acceptor, e.g. triethylamine or potassium carbonate or a combination thereof, in a suitable solvent, e.g. acetonitrile, and at about the reflux temperature thereof.

The compound of the formula (III) can be prepared in situ from an acid addition salt thereof by using a molar excess of the acid acceptor.

50 The starting materials of the formula (VIII) may be prepared by conventional methods such as by hydroxy group functional transformation of alcohols of formula (VIIIa) :

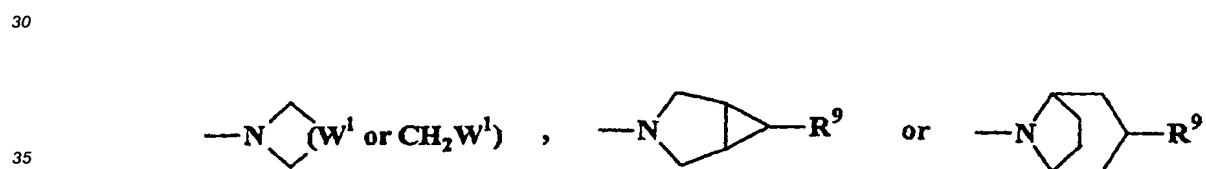
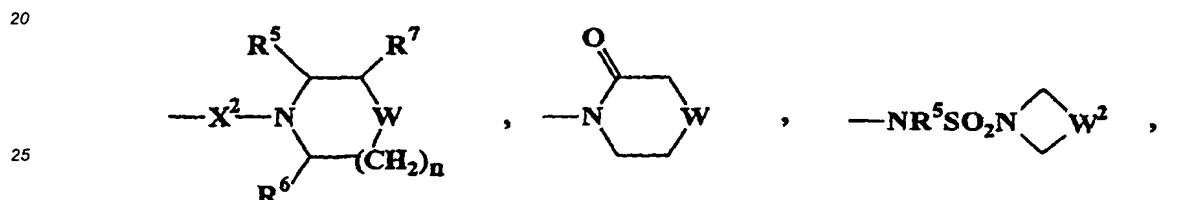


where R and R¹ are as described earlier for compounds of formula (I), for example where Z³ is methanesulphonyloxy by reaction of an alcohol of formula (VIIa) with methanesulphonyl chloride in the presence of a suitable acid acceptor such as triethylamine. The alcohol of formula (VIIa) may be prepared by reduction of an aldehyde of formula (II) as defined above in Method 1, using conventional methods, such as those described in J.March, Advanced Organic Chemistry, 3rd edition, Wiley Interscience, for example by reaction with a suitable reducing agent such as zinc borohydride in a suitable solvent such as tetrahydrofuran.

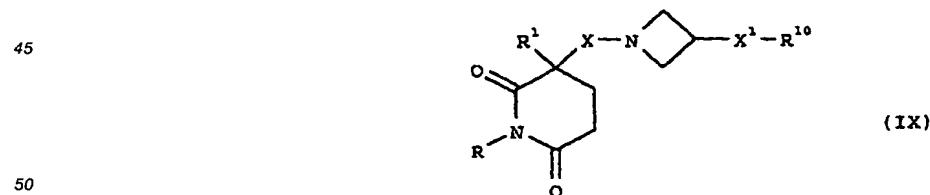
5) The compounds of the formula (I) where R¹ is phenyl and X, X¹, R and R² are as previously defined for a compound of the formula (I) can be prepared by hydrogenolysis of a compound of the formula (I) where R¹ is phenyl substituted by chloro, bromo or iodo and X, X¹, R and R² are as previously defined for a compound of the formula (I).

10) In a typical procedure the hydrogenolysis is carried out in ammoniacal ethanol using a suitable catalyst, e.g. Raney nickel or, preferably, palladium-on-carbon, at about 50°C and under an atmosphere of hydrogen at about 345kPa (50 psi).

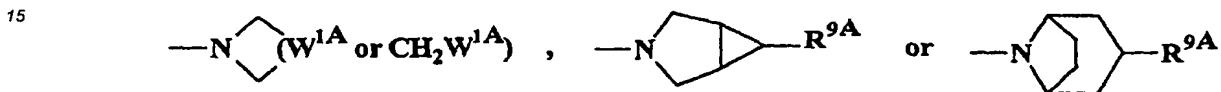
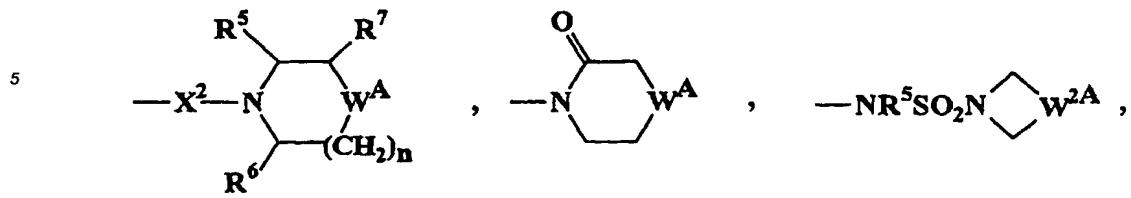
15) The compounds of the formula (I) where R² is a group of the formula: -NHR⁴, (C₃-C₇ cycloalkyl-C₁-C₄ alkyl)HN-,



40) R⁹ is -NHR⁵, W is NH or CHNHR⁵, W¹ is CHNHR⁵, W² is W¹, -CH₂W¹-, -CH₂WCH₂- or -CH₂CH₂WCH₂-, and X, X¹, X², R, R¹, R⁵, R⁶, R⁷ and n are as previously defined for a compound of the formula (I), can be prepared by deprotection of a compound of the formula (IX):-



55) where R¹⁰ is a group of the formula: -NZ⁴R⁴, (C₃-C₇, cycloalkyl-C₁-C₄ alkyl)Z⁴N-,



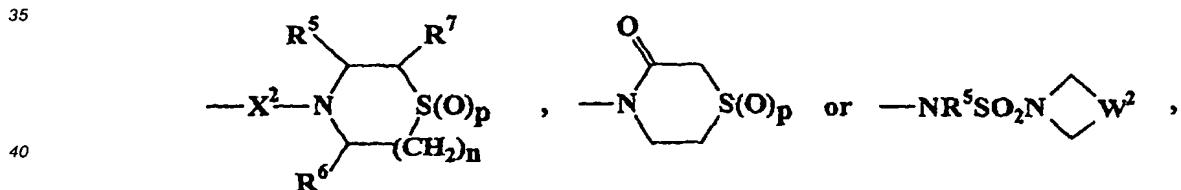
20 , respectively, R^{9A} is -NZ⁴R⁵, W^A is NZ⁴ or CHNZ⁴R⁵, W^{1A} is CHNZ⁴R⁵, W^{2A} is W^{1A}, -CH₂W^{1A}-, -CH₂W^ACH₂- or -CH₂CH₂W^ACH₂-; X, X¹, X², R, A, R¹, R⁴, R⁵, R⁶, R⁷, m and n are as previously defined for a compound of the formula (I) and Z⁴ is a suitable protecting group, e.g. t-butoxycarbonyl (e.g. a compound of the formula (I) where W is NCO₂C(CH₃)₃ or R⁹ is -NR⁵CO₂C(CH₃)₃) or benzyloxycarbonyl.

25 Suitable protecting groups that may be used in this Method, together with methods for deprotection, are well known to the skilled person, e.g. see Greene *et al*, "Protective Groups in Organic Synthesis", Second Edition, 1991, Wiley-Interscience.

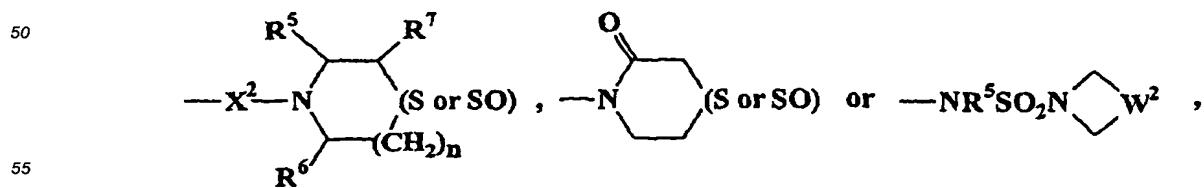
In a typical procedure where Z⁴ is t-butoxycarbonyl, the deprotection can be carried out using trifluoroacetic acid in a suitable solvent, e.g. dichloromethane, at room temperature.

30 The starting materials of the formula (IX) can be prepared by conventional methods such as by appropriate adaptation of the Methods described herein for preparing the compounds of the formula (I).

6) The compounds of the formula (I) where R² is a group of the formula:-



45 where p is 1 or 2, W² is -CH₂S(O)_pCH₂- or -CH₂CH₂S(O)_pCH₂- and X, X¹, X², R, R¹, R⁵, R⁶, R⁷ and n are as previously defined for a compound of the formula (I) can be prepared by oxidation of a compound of the formula (I) where R² is a group of the formula:-



, as appropriate, wherein W^2 is $-\text{CH}_2(\text{S or SO})\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2(\text{S or SO})\text{CH}_2-$, and $X, X^1, X^2, R, R^1, R^5, R^6, R^7$ and n are as previously defined for a compound of the formula (I). The oxidation is carried out with at least one molar equivalent of a suitable oxidising agent when converting a sulfoxide to a sulphone, at least two molar equivalents of a suitable oxidising agent when converting a sulphide to a sulphone and substantially one molar equivalent of a suitable oxidising agent for the conversion of a sulphide to a sulfoxide.

5

Suitable oxidising agents and conditions for this purpose are aqueous hydrogen peroxide solution under basic conditions (e.g. in the presence of potassium carbonate, acetonitrile and using methanol as the solvent) or m-chloroperbenzoic acid in a suitable solvent, e.g. dichloromethane.

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7) The compounds of the formula (I) where R^2 is a group of the formula:-

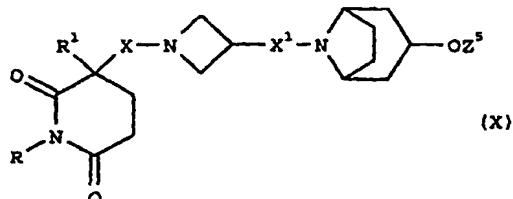
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and X, X^1, R and R^1 are as previously defined for a compound of the formula (I), can be prepared by deprotection of a compound of the formula (X):-

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where Z^5 is a suitable protecting group, e.g. acetyl (i.e. a compound of the formula (I) where R^8 is acetoxy) or tetrahydropyran-2-yl, and X, X^1, R and R^1 are as previously defined for a compound of the formula (I).

Suitable protecting groups that may be used for this Method, together with methods for deprotection, are well known to the skilled person, e.g. see Greene *et al*, "Protective Groups in Organic Synthesis", Second Edition, 1991, Wiley-Interscience.

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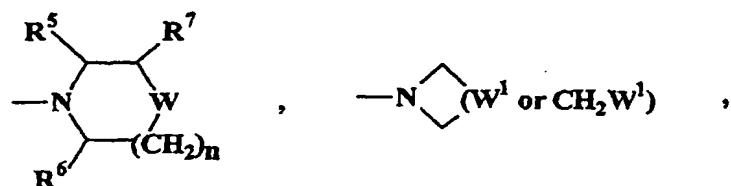
In a typical procedure where Z^5 is acetyl the deprotection can be carried out using an aqueous alcoholic solution of a suitable strong base, e.g. sodium hydroxide. The reaction is typically carried out in aqueous methanol at about room temperature.

The starting materials of the formula (X) can be prepared by conventional methods such as by adaptation of the Methods described herein for preparing the compounds of the formula (I).

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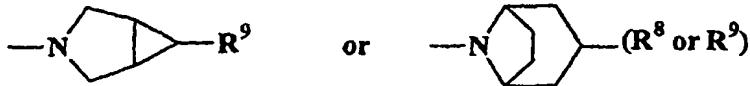
8) The compounds of the formula (I) where X^1 is a direct link and R^2 is $-\text{NR}^3\text{R}^4$, ($\text{C}_3\text{-C}_7$ cycloalkyl- $\text{C}_1\text{-C}_4$ alkyl) $\text{R}^5\text{N}-$, or is a group of the formula:-

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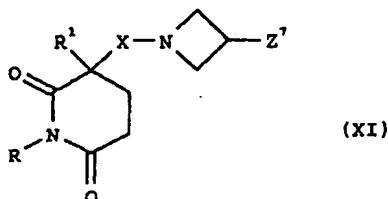
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10 and X, W, W¹, R, R¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and n are as previously defined for a compound of the formula (I), can be prepared by reaction of a compound of the formula (XI):-

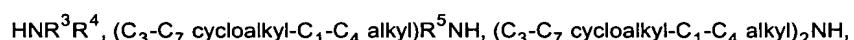
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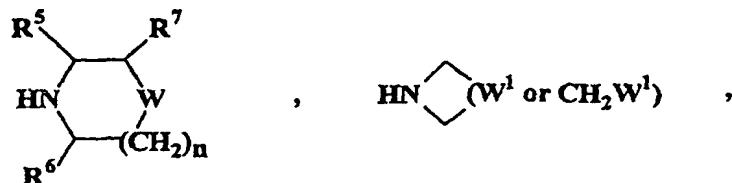
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where X, R and R¹ are as previously defined for a compound of the formula (I) and Z⁷ is a suitable leaving group, e.g. methanesulphonyloxy or p-toluenesulphonyloxy, with a compound of the formula:

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50 respectively, where W, W¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and n are as previously defined for a compound of the formula (I).

In a typical procedure, the reaction is carried out using an excess of the amine and in a suitable solvent, e.g. acetonitrile or dichloromethane, and at the reflux temperature of the solvent. Alternatively, a further suitable acid acceptor, e.g. potassium carbonate, can be added to the reaction mixture.

55

The starting amines can be prepared by conventional methods.

The starting materials of the formula (XI) can also be prepared by conventional methods such as by reductive amination using as starting materials a compound of the formula (II) and ammonia to prepare the corresponding primary amine, reaction of the amine with epichlorohydrin or 1,3-dichloropropan-2-ol to prepare the corresponding

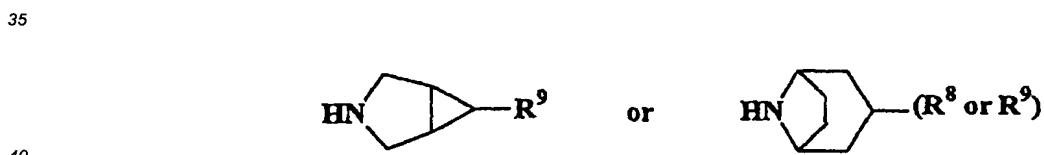
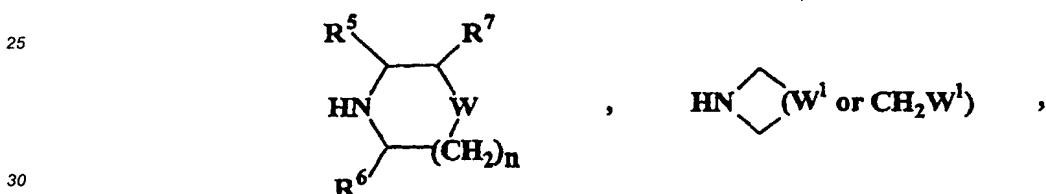
azetidin-3-ol derivative, followed by hydroxy functional group interconversion to provide a compound of the formula (XI).

5 9) The compounds of the formula (I) where X, X¹, R, R¹ and R² are as previously defined for Method (8) can be prepared by reductive amination using as starting materials a compound of the formula (XII):-



where X, R and R¹ are as previously defined for a compound of the formula (I), and a compound of the formula:-

20 HNR^3R^4 , $(\text{C}_3\text{-C}_7 \text{ cycloalkyl-C}_1\text{-C}_4 \text{ alkyl})\text{R}^5\text{NH}$,



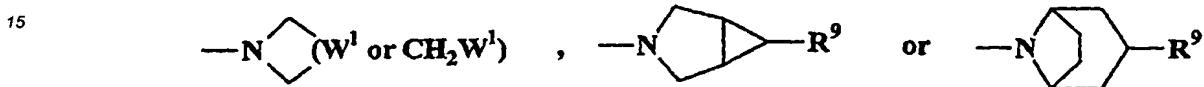
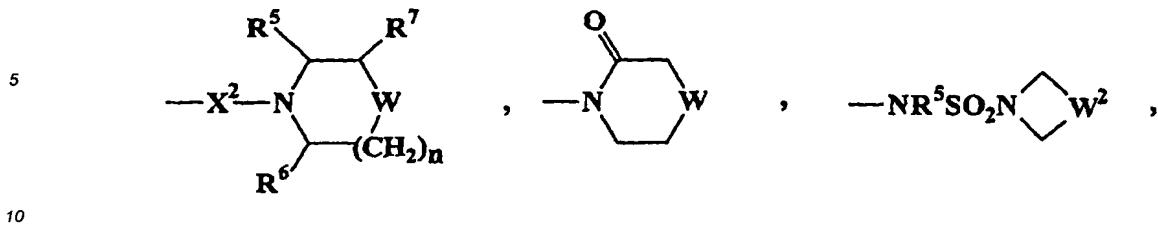
45 , as appropriate, or an acid addition salt thereof, where W, W¹, R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and n are as previously defined for a compound of the formula (I). The reaction is preferably carried out in the presence of a suitable acid, e.g. acetic acid.

A typical procedure that can be followed is described in Method (1).

If a primary amine is used, the reaction proceeds via an imine intermediate. If a secondary amine is used, the reaction proceeds via an intermediate iminium species (cf. a compound of the formula (IIIA)). Both the imine and iminium species may be stable and isolatable. The reaction is preferably carried out without isolation of the imine or iminium salt intermediate in which case it is reduced in situ to provide a compound of the formula (I).

50 The starting materials of the formula (XII) can be prepared by oxidation of a compound of the formula (XI; Z⁷ is OH) using a suitable oxidation regime, such as a Swern oxidation.

55 10) Certain compounds of the formula (I) can be prepared by derivatisation of certain amines of the formula (I). For example, a compound of the formula (I) wherein R² is



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wherein W is NH or CHNHR⁵, W¹ is CHNHR⁵, W² is W¹, -CH₂W¹-, -CH₂WCH₂- or -CH₂CH₂WCH₂-, or R⁹ is -NHR⁵ and X, X¹, X², R, R¹, R⁵, R⁶, R⁷ and n are as previously defined for a compound of the formula (I), may be converted to

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(a) a compound of the formula (I) wherein W is NR⁵ or CHNR⁵R⁶, W¹ is CHNR⁵R⁶ or R⁹ is -NHR⁵, or an acid addition salt thereof, as appropriate, wherein R⁵ and R⁶ are as previously defined for a compound of the formula (I) with the provisos that R⁵ is not H and it has a methylene group bonded to the nitrogen atom, by reductive amination with an aldehyde of the formula (C₁-C₃ alkyl)CHO or (C₃-C₇ cycloalkyl-C₁-C₃ alkyl)CHO, said C₁-C₃ alkyl and C₃-C₇ cycloalkyl-C₁-C₃ alkyl being optionally substituted by fluoro. Suitable conditions for this conversion are described in Method (1);

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(b) a compound of the formula (I) wherein W is NCONHR⁶ or CHNR⁵CONHR⁶, W¹ is CHNR⁵CONHR⁶ or R⁹ is -NR⁵CONHR⁶, as appropriate, wherein R⁵ and R⁶ are as previously defined for a compound of the formula (I) with the proviso that R⁶ is not H, by reaction with an isocyanate of the formula:



wherein R⁶ is as previously defined for this Method.

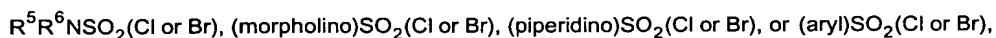
The reaction is typically carried out using a suitable solvent, e.g. dichloromethane or tetrahydrofuran;

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(c) a compound of the formula (I) wherein W is NSO₂CF₃ or CHNR⁵SO₂CF₃, W¹ is CHNR⁵SO₂CF₃ or R⁹ is -NR⁵SO₂CF₃, as appropriate, wherein R⁵ is as previously defined for a compound of the formula (I), by reaction with trifluoromethanesulphonyl chloride or trifluoromethanesulphonic anhydride, optionally in the presence of a suitable acid acceptor, e.g. triethylamine, pyridine or potassium carbonate. The reaction is typically carried out in a suitable organic solvent, e.g. dichloromethane or acetonitrile;

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(d) a compound of the formula (I) wherein W is NSO₂(C₁-C₄ alkyl), NSO₂NR⁵R⁶, NSO₂ (morpholino), NSO₂ (piperidino), NSO₂(aryl), CHNR⁵(SO₂ C₁-C₄ alkyl) or CHNR⁵SO₂NR⁵R⁶, W¹ is CHNR⁵(SO₂ C₁-C₄ alkyl) or CHNR⁵SO₂NR⁵R⁶, or R⁹ is -NR⁵(SO₂ C₁-C₄ alkyl) or -NR⁵SO₂NR⁵R⁶, as appropriate, wherein R⁵ and R⁶ are as previously defined for a compound of the formula (I), by reaction with a C₁-C₄ alkanesulphonyl chloride or bromide, a C₁-C₄ alkanesulphonic anhydride or a compound of the formula:



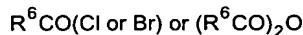
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, as appropriate, optionally in the presence of a suitable acid acceptor, e.g. triethylamine.
The reaction is typically carried out in a suitable organic solvent, e.g. dichloromethane, at from 0°C to

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room temperature;

5 (e) a compound of the formula (I) wherein W is NCOR^6 or $\text{CHNR}^5\text{COR}^6$, W^1 is $\text{CHNR}^5\text{COR}^6$ or R^9 is $-\text{NR}^5\text{COR}^6$, as appropriate, wherein R^5 and R^6 are as previously defined for a compound of the formula (I) with the proviso that R^6 is not H, by reaction with a compound of the formula:



10 wherein R^6 is as previously defined for this Method, optionally in the presence of a suitable acid acceptor, e.g. triethylamine.

The reaction is typically carried out in a suitable organic solvent, e.g. dichloromethane, at from 0°C to room temperature;

15 (f) a compound of the formula (I) wherein W, W^1 or R^9 is as previously defined for Method 10(e), as appropriate, by condensation with a compound of the formula:-



20 wherein R^6 is as previously defined for this Method. The reaction can be performed under conventional conditions, e.g. using 1,1'-carbonyldiimidazole or 1-hydroxybenzotriazole/1,3-dicyclohexylcarbodiimide to generate activated intermediates;

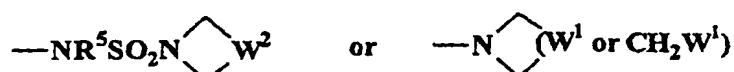
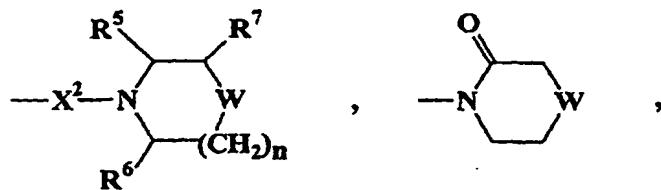
or

25 (g) a compound of the formula (I) where W is $\text{NSO}_2\text{NR}^5\text{R}^6$ or $\text{CHNR}^5\text{SO}_2\text{NR}^5\text{R}^6$, W^1 is $\text{CHNR}^5\text{SO}_2\text{NR}^5\text{R}^6$ or R^9 is $-\text{NR}^5\text{SO}_2\text{NR}^5\text{R}^6$, as appropriate, wherein R^5 and R^6 are as previously defined for a compound of the formula (I), by reaction with a compound of the formula:



The reaction is typically carried out at an elevated temperature in a suitable solvent, e.g. 1,4-dioxane.

35 11) The compounds of the formula (I) wherein R^2 is:



55 wherein W and W^1 are CHCO_2H and W^2 is W^1 , $-\text{CH}_2\text{W}^1$, $-\text{CH}_2\text{WCH}_2$ or $-\text{CH}_2\text{CH}_2\text{WCH}_2$ and X, X^1 , X^2 , R, R^1 , R^2 , R^5 , R^6 , R^7 and n are as previously defined for a compound of the formula (I), may be prepared by hydrolysis of a compound of the formula (I) wherein

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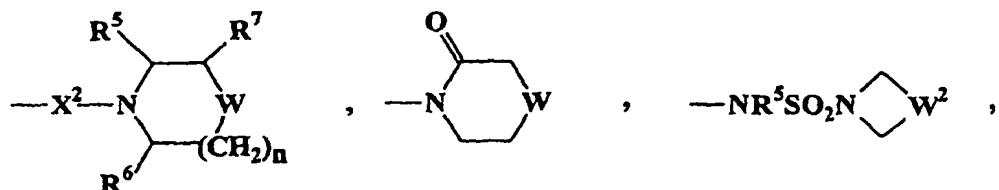
W and W¹ are CHCO₂(C₁-C₄ alkyl), W² is W¹, -CH₂W¹-, -CH₂WCH₂- or -CH₂CH₂WCH₂- and X, X¹, X², R, R¹, R², R⁵, R⁶, R⁷ and n are as previously defined for a compound of the formula (I). Preferably, W and W¹ are CHCO₂CH₃ or CH₂CO₂CH₂CH₃.

5 The hydrolysis is typically carried out using an aqueous solution of a suitable acid or base, e.g. a mineral acid such as hydrochloric or sulphuric acid or a base such as sodium or potassium hydroxide, optionally in the presence of a suitable organic co-solvent, e.g. methanol or ethanol.

12) The compounds of the formula (I) wherein R² is

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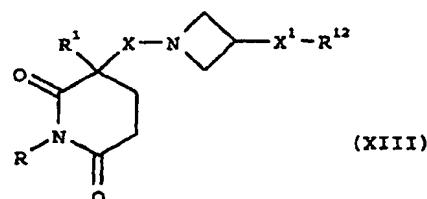


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wherein W and W¹ are CHNR⁵R⁶, W² is W¹, -CH₂W¹-, -CH₂WCH₂- or -CH₂CH₂WCH₂-, R⁹ is -NR⁵R⁶ and X, X¹, X², R, R¹, R², R⁵, R⁶, R⁷ and n are as previously defined for a compound of the formula (I) may be prepared by reaction of a compound of the formula (XIII):

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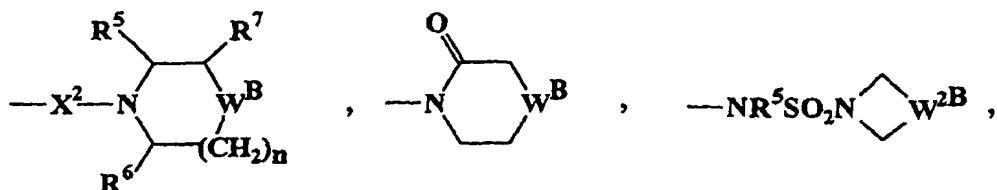


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wherein R¹² is

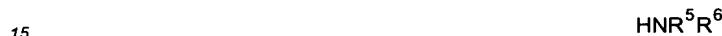
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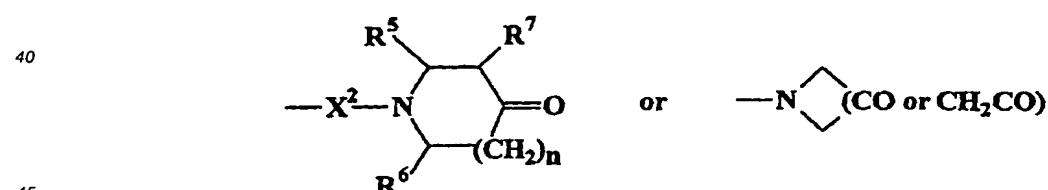
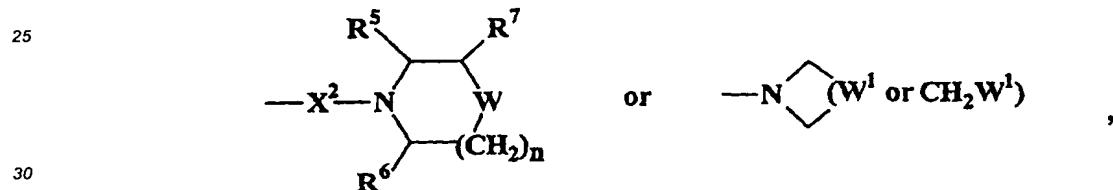
10 wherein W^B and W^{1B} are CHZ^8 , W^{2B} is W^{1B} , $-CH_2W^{1B}$, $-CH_2W^BCH_2$ - or $-CH_2CH_2W^BCH_2$ -, Z^8 is a suitable leaving group, e.g. halo, (preferably chloro or bromo), methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy, and X , X^1 , X^2 , R , R^1 , R^5 , R^6 , R^7 and n are as previously defined for a compound of the formula (I), with a compound of the formula:



20 wherein R^5 and R^6 are as previously defined for a compound of the formula (I), optionally in the presence of a suitable additional acid acceptor, e.g. triethylamine or potassium carbonate.

25 The reaction is typically carried out in a suitable solvent such as acetonitrile.

20 13) The compounds of the formula (I) wherein R^2 is



55 wherein R^5 and R^6 are as previously defined for a compound of the formula (I).

55 [0032] Conventional conditions are used such as those described for Method (1). Again, the intermediate imine or iminium species formed may be stable or isolatable. The reaction is preferably carried out without isolation of this intermediate in which case it is reduced *in situ* to provide a compound of the formula (I).

55 [0033] All of the above reactions and the preparations of novel starting materials used in the preceding methods are

conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well known to those skilled in the art with reference to literature precedents and the Examples and Preparations hereto.

[0034] A pharmaceutically acceptable acid addition or base salt of a compound of the formula (I) may be readily prepared by mixing together solutions of a compound of the formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

[0035] The affinity of the compounds of formula (I) and their salts for the human NK₁ receptor can be tested *in vitro* by testing their ability to inhibit [³H]-Substance P binding to membranes prepared from the human IM9 cell line expressing the human NK₁ receptor using a modification of the method described in McLean, S. *et al*, *J. Pharm. Exp. Ther.*, 267, 472-9 (1993) in which whole cells were used.

[0036] The affinity of the compounds of formula (I) and their salts for the human NK₂ receptor can be tested *in vitro* by testing their ability to compete with [³H] or [¹²⁵I]NKA (neurokinin A) for binding to membranes prepared from Chinese hamster ovary cells expressing the cloned human NK₂ receptor. In this method, washed Chinese hamster ovary cell membranes are prepared as described for the previous method where IM9 cells are used instead. The membranes are incubated (90 min, 25°C) with [³H] or [¹²⁵I] NKA and with a range of concentrations of the test compound. Non-specific binding was determined in the presence of 10μM NKA.

[0037] The NK₂ receptor antagonist activity of the compounds of the formula (I) can be tested, *in vitro*, by testing their ability to antagonise the contractile effects of the selective NK₂ receptor agonist [β Ala⁸]NKA₍₄₋₁₀₎ in the rabbit pulmonary artery, using the method of Patacchini and Maggi, *Eur. J. Pharmacol.*, 236, 31-37 (1993).

[0038] The compounds of the formula (I) and their salts can be tested for NK₂ receptor antagonist activity, *in vivo*, by testing their ability to inhibit bronchoconstriction induced by [β Ala⁸]NKA₍₄₋₁₀₎ in the anaesthetised guinea pig, using the method described by Murai *et al*, *J. Pharm. Exp. Ther.*, 262, 403-408 (1992) or Metcalfe *et al*, *Br. J. Pharmacol.*, 112, 563P (1994).

[0039] The compounds of the formula (I) and their salts can be tested for NK₃ receptor antagonist activity, *in vitro*, by testing their ability to antagonise the contractile effects of the selective NK₃ receptor agonist senktide in the guinea-pig ileum using the method of Maggi *et al*, *Br. J. Pharmacol.*, 101, 996-1000 (1990).

[0040] For human use, the compounds of the formula (I) and their salts can be administered alone, but will generally be administered in admixture with a pharmaceutically acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually, in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

[0041] For oral and parenteral administration to human patients, the daily dosage level of the compounds of the formula (I) and their salts will be from 0.001 to 20, preferably from 0.01 to 20, more preferably from 0.1 to 10, and most preferably from 0.5 to 5, mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 50 to 200, mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[0042] Alternatively, the compounds of the formula (I) can be administered by inhalation or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

[0043] It is to be appreciated that reference to treatment includes prophylaxis as well as the alleviation of established symptoms of the disease.

[0044] Thus the invention further provides:-

- i) a pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier;
- ii) a compound of the formula (I), or a pharmaceutically acceptable salt or composition thereof, for use as a medicament;
- iii) the use of a compound of the formula (I), or of a pharmaceutically acceptable salt or composition thereof, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin

5 acting at the human NK₁, NK₂ or NK₃ receptor, or a combination of two or more thereof;

10 iv) use as in (iii) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain;

15 v) a method of treatment of a human to treat a disease by producing an antagonist effect on a tachykinin acting at the human NK₁, NK₂ or NK₃ receptor, or a combination of two or more thereof, which comprises treating said human with an effective amount of a compound of the formula (I) or with a pharmaceutically acceptable salt or composition thereof;

20 vi) a method as in (v) where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, an urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a burn, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain; and

25 vii) a compound of the formula (II), (IIIA), (V), (VI), (VII), (VIII), (VIIIA), (IX), (X), (XI), (XII) and (XIII).

[0045] The following Examples illustrate the preparation of the compounds of the formula (I):

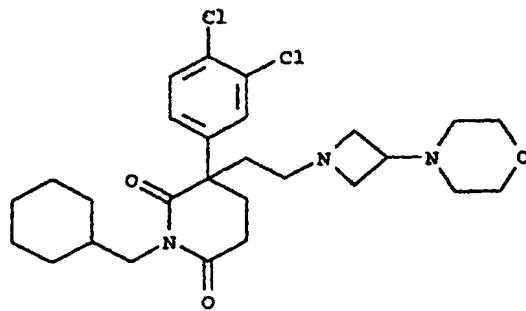
25

EXAMPLE 1:

1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-morpholinoazetidin-1-yl)ethyl)glutarimide

30

[0046]



1(a) 2-(3,4-Dichlorophenyl)pent-4-enenitrile

50

[0047] To a stirred solution of 3,4-dichlorophenylacetonitrile (800g, 4.3 mol) in cyclohexane (161) at room temperature was carefully added aqueous NaOH solution (1.6kg NaOH in 81 of water). The addition caused the temperature of the reaction to increase to 50°C. Allyl bromide (572g, 1.1 mol equivalents) and tetra-n-butylammonium chloride hydrate (40g, 0.03 mol equivalents) were then added and the reaction was stirred for 1 hr at 50°C. The aqueous phase was then separated and the organic layer washed with water (10l), then filtered through silica gel (1kg) under reduced pressure to give a yellow filtrate solution. Removal of the solvent from said filtrate *in vacuo* gave the title compound as an oil (960g) of 70% purity, which was used without further purification.

55

TLC R_f = 0.71 (silica, diethyl ether:hexane, 1:1).

LRMS m/z = 226 (m)⁺.

¹H NMR (CDCl₃): 2.6-2.75 (m, 2H); 3.85 (t, 1H); 5.1-5.25 (m, 2H); 5.7-5.9 (m, 1H), 7.2-7.25 (m, 1H), 7.5-7.55 (m, 2H) ppm.

1(b) 4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid

[0048] To a stirred suspension of 60% w/w NaH oil dispersion (231g) in tetrahydrofuran (THF) (171) under nitrogen at -10°C was added a solution of 3-bromopropanoic acid (806.5g) in THF dropwise over 3 hours. The reaction was allowed to warm to room temperature over 22 hours, and then cooled to -10°C. Simultaneously, a solution of the compound from 1(a) above (1633.5g) in THF (2.5l) was added dropwise over 2 hours to a stirred suspension of 60% w/w NaH oil dispersion (221g) in THF (2.5l) under nitrogen at -10°C. When the addition was complete, this second reaction was allowed to warm to room temperature over 18 hours. The reaction was then cooled to -10°C and cannulated into the above 3-bromopropanoic acid sodium salt mixture over 3 hours. The reaction mixture was heated to 50°C for 5 hours, then cooled, poured into water (8l) and basified to pH 9.3 using aqueous NaHCO₃ solution. This mixture was washed with dichloromethane (5 x 2l) and the aqueous portion acidified to pH 1.0 using concentrated HCl. The aqueous solution was extracted with dichloromethane (4 x 2.5l) and the organic layers were combined, dried using anhydrous MgSO₄, filtered and the filtrate concentrated *in vacuo* to give a yellow oil. This oil was then triturated with hexane (1.5l) to give the title compound as a cream solid (1155.3g) which was used without any further purification.

TLC R_f = 0.42 (silica, methanol:dichloromethane 1:9).

LRMS m/z = 316 (m + NH₄)⁺.

¹H NMR (CDCl₃): 2.15-2.8 (m, 6H); 5.1-5.25 (m, 2H); 5.55-5.7 (m, 1H); 7.2-7.25 (m, 1H); 7.5-7.55 (m, 2H) ppm.

1(c) 3-Allyl-3-(3,4-dichlorophenyl)-(1H)-glutarimide

[0049] A solution of the compound from 1(b) above (10g), formic acid (12ml) and concentrated HCl (6ml) in N,N-dimethylformamide (DMF) (69ml) was heated at 145°C for 48 hours. The solution was cooled to room temperature and water (100ml) was added. The mixture was basified with 15% aqueous Na₂CO₃ solution until an oily precipitate formed, and then extracted with ethyl acetate (2x100ml). The combined organic phases were then dried over anhydrous Na₂SO₄, filtered and the solvent removed *in vacuo* to give an oil, which was purified by flash chromatography (silica, ethyl acetate) to give the title compound (4.3g).

LRMS m/z 298 (m+1)⁺.

¹H NMR (d⁶-DMSO): 2.1-2.2 (m, 2H); 2.3-2.7 (m, 4H); 5.0-5.1 (m, 2H); 5.5-5.7 (m, 1H); 7.2-7.6 (m, 3H); 10.95 (s, br, 1H) ppm.

1(d) 3-Allyl-1-cyclohexylmethyl-3-(3,4-dichlorophenyl)glutarimide

[0050] To a mixture of NaH (80mg, 60% dispersion in oil) in DMF (10ml), cooled in an ice-bath under nitrogen, was added the compound of 1(c) above (0.5g) and the mixture was stirred for 45 minutes. Cyclohexylmethyl bromide (0.26ml) was then added and the reaction mixture was heated to 50°C for 18 hours. The reaction was cooled to room temperature and the solvent was removed *in vacuo*. Water (20ml) was added and the mixture extracted with ethyl acetate (2 x 20ml). The combined organics were washed with brine (40ml) and dried over anhydrous Na₂SO₄. The solution was then filtered, and the solvent removed *in vacuo* to give an oil which was purified by flash chromatography (silica, diethyl ether:hexane 1:4) to give the title compound.

TLC R_f = 0.46 (silica, diethyl ether: hexane, 1:1).

LRMS m/z = 394 (m+1)⁺.

¹H NMR (CDCl₃): 0.9-1.1 (m, 2H); 1.15-1.3 (m, 3H); 1.4-1.75 (m, 6H); 2.15-2.8 (m, 6H); 3.7 (d, 2H); 5.0-5.15 (m, 2H); 5.55-5.65 (m, 1H); 7.1-7.4 (m, 3H) ppm.

1(e) 1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

[0051] Into a solution of the compound of 1(d) above (0.45g) in methanol (25ml) under nitrogen at -78°C was bubbled ozone at rate of 50ml / minute (using a charge of 1.5A to generate ozone from oxygen) for 20 minutes. The current was then reduced to zero, and oxygen was bubbled through the reaction at a rate of 5ml / minute for 10 minutes. The oxygen supply was then removed and a solution of dimethyl sulphide (DMS) (0.83ml) in methanol (3ml) was added dropwise, and the reaction was left to warm to room temperature for 18 hours. The solvent was removed *in vacuo* and the mixture was partitioned between ethyl acetate (20ml) and water (20ml). The organic layer was then dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo* to give a residue which was purified by flash chromatography (silica, diethyl ether: hexane, 1:1) to give the title compound (0.265g).

LRMS m/z = 396 (m+1)⁺.

¹H NMR (CDCl₃): 0.95-1.3 (m, 5H); 1.5-1.8 (m, 6H); 2.2-2.4 (m, 2H); 2.55-2.85 (m, 3H); 3.2 (d, 1H); 3.75 (d, 2H); 7.05-7.5 (m, 3H); 9.6 (s, 1H) ppm.

1(f) 1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-morpholinoazetidin-1-yl)ethyl)glutarimide

[0052] To a solution of the aldehyde product of 1(e) above (0.23g) and 3-morpholinoazetidine dihydrochloride (0.14g) (Preparation 1) in THF (30ml) under nitrogen was added triethylamine (0.25g). After 90 minutes, sodium triacetoxymethane (0.16g) was added, followed immediately by glacial acetic acid (0.09ml), and the mixture was stirred for 18 hours. Saturated aqueous NaHCO₃ solution (10ml) was then added and the mixture extracted with ethyl acetate (2 x 20ml). The combined organic layers were washed with water (50ml) and dried over anhydrous MgSO₄. The solution was filtered, the solvent removed *in vacuo* and the residue purified by column chromatography (silica, dichloromethane: methanol, 19:1) to give the title compound (0.273g).

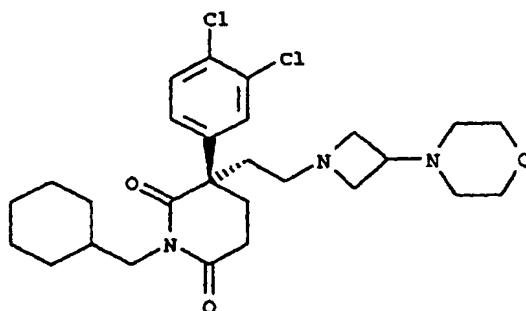
TLC R_f = 0.16 (silica, dichloromethane:methanol, 19:1).

LRMS m/z = 522 (m+1)⁺.

¹H NMR (CDCl₃): 0.95-1.3 (m, 5H); 1.5-1.8 (m, 6H); 1.85-2.1 (m, 2H); 2.1-3.0 (m, 13H); 3.4-3.5 (m, 2H), 3.7-3.75 (m, 6H); 7.1-7.45 (m, 3H) ppm.

15 EXAMPLE 2: 3(S)-1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-morpholinoazetidin-1-yl)ethyl)glutarimide

[0053]

2(a) 4(S)-4-Cyano-4-(3,4-dichlorophenyl)hept-6-enoic acid35 (i) R-(+)-1-(1-naphthyl)ethylamine salt

[0054] To a solution of the compound of Example 1(b) above (16g) in ethyl acetate (50ml) was added R-(+)-1-(1-naphthyl)ethylamine (4.8g). The solution was stirred for 30 minutes at room temperature and then the solvent removed *in vacuo* to give a gum. This was partially dissolved in hexane : diethyl ether (4:1, 150ml) and the sides of the flask 40 scratched to induce crystallisation. The white solid that formed was filtered off and crystallised 3 times from ethyl acetate to give the title compound (4.9g).

m.p. 153-4°C.

[α]₅₈₉ = -7.1° (25°C, c = 0.0012).

¹H NMR (CDCl₃): 1.6 (d, 3H); 2.0-2.2 (m, 2H); 2.25-2.5 (m, 2H); 2.5-2.7 (m, 2H); 3.8-4.1 (s, br, 3H); 5.0-5.2 (m, 3H); 45 5.5-5.7 (m, 1H); 7.15-7.25 (m, 1H); 7.4-7.6 (m, 6H); 7.75 (d, 1H); 7.9 (d, 1H); 8.1 (d, 1H) ppm.

(ii) Free Acid

[0055] To a stirred solution of the R-(+)-1-(1-naphthyl)ethylamine salt from (i) above (5.5g) in dichloromethane (100ml) was added 1N aqueous HCl (100ml). The aqueous layer was then removed and the organic portion washed with 1N aqueous HCl (70ml). The organic layer was dried over MgSO₄, filtered and the filtrate reduced *in vacuo* to give the title compound (3.6g).

LRMS m/z = 316 (m+NH₄)⁺.

¹H NMR (CDCl₃): 2.15-2.8 (m, 6H); 5.1-5.25 (m, 2H); 5.55-5.7 (m, 1H); 7.2-7.25 (m, 1H); 7.5-7.55 (m, 2H) ppm.

55 2(b) 3(S)-Allyl-3-(3,4-dichlorophenyl)-(1H)-glutarimide

[0056] This compound was made in the same way as described in Example 1(c) above, using the chiral acid of

Example 2(a)(ii) above.

TLC R_f = 0.87 (silica, ethyl acetate : hexane, 1:3).

m.p. 137-8°C.

$[\alpha]_{589} = 178^\circ$ (25°C, c = 0.00034).

5 ^1H NMR (CDCl_3): 2.1-2.7 (m, 6H); 5.1-5.2 (m, 2H); 5.55-5.65 (m, 1H); 7.2-7.6 (m, 3H) ppm.

2(c) 3(S)-3-Allyl-1-cyclohexylmethyl-3-(3,4-dichlorophenyl)-glutarimide

10 [0057] This was made in the same way as described in Example 1(d) above, using the chiral glutarimide of Example 2(b) above.

LRMS and ^1H NMR data corresponded with that of Example 1(d) above.

2(d) 3(S)-1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

15 [0058] This was made in the same way as described in Example 1(e) above, using the chiral glutarimide of Example 2(c) above.

LRMS and ^1H NMR data corresponded with that of Example 1(e) above.

20 2(e) 3(S)-1-Cyclohexylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-morpholinoazetidin-1-yl)ethyl)glutarimide

[0059] This was made by the same method to that described above in 1(f), using the chiral aldehyde of 2(d) above. LRMS m/z = 522 ($m+1$)⁺.

Found : C 60.98%; H 7.40%; N 7.43 %. $\text{C}_{27}\text{H}_{37}\text{Cl}_2\text{N}_3\text{O}_3$. 0.5 H_2O requires C 61.0%; H 7.03%; N 7.90%.

25 ^1H NMR (CDCl_3): 0.95-1.3 (m, 5H); 1.5-1.8 (m, 6H); 1.85-2.1 (m, 2H); 2.1-3.0 (m, 13H), 3.4-3.5 (m, 2H); 3.7-3.75 (m, 6H); 7.1-7.45 (m, 3H) ppm.

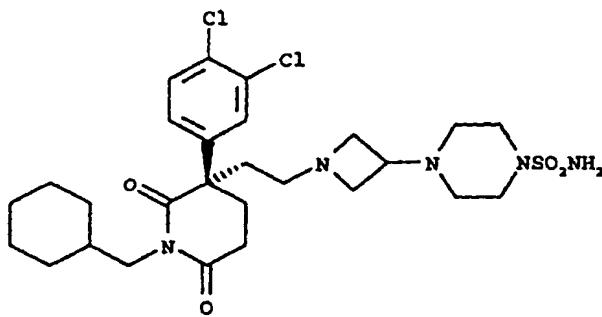
$[\alpha]_{589} = 90.4^\circ$ (25°C, c = 0.00022).

EXAMPLE 3:

30 3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclohexylmethyl-3-(3,4-dichlorophenyl)glutarimide

[0060]

35



50 [0061] This was made in the same way as described in Example 2(e) above, using 3-(4-aminosulphonylpiperazin-1-yl)azetidine bis trifluoroacetate (Preparation 2). LRMS m/z = 600 ($m+1$)⁺.

1H NMR (CDCl_3): 0.9-1.3 (m, 5H); 1.4-1.8 (m, 7H); 1.85-2.15 (m, 2H); 2.2-2.5 (m, 8H); 2.55-2.7 (m, 1H); 2.85-3.1 (m, 3H), 3.2-3.25 (m, 4H); 3.4-3.5 (m, 2H); 3.7-3.75 (m, 2H); 4.3 (s, br, 2H); 7.05-7.45 (m, 3H) ppm.

55

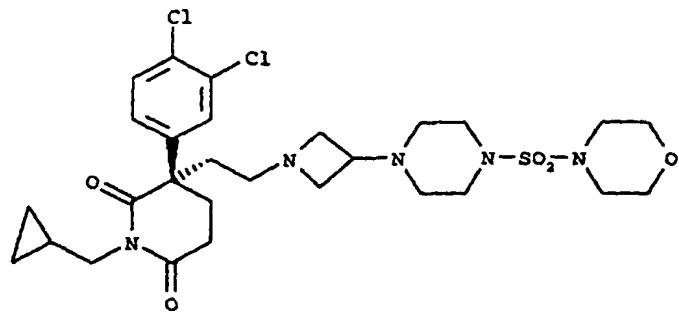
EXAMPLE 4:

3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-morpholinosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)glutarimide

5

[0062]

10



15

20

4(a) 3(S)-3-Allyl-1-cyclopropylmethyl-3-(3,4-dichlorophenyl)glutarimide

25

[0063] This was made in the same way as that described in Example 2(c) above, using cyclopropylmethyl bromide. LRMS m/z = 352 (m+1)⁺.

¹H NMR (CDCl₃): 0.3-0.55 (m, 4H); 0.95-1.1 (m, 1H); 2.2-2.9 (m, 6H); 3.3 (d, 2H); 5.05-5.2 (m, 2H); 5.6-5.75 (m, 1H); 7.1-7.45 (m, 3H) ppm.

30

4(b) 1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

35

[0064] This was made in the same way as that described in Example 2(d) above, using the compound of Example 4(a) above.

LRMS m/z = 354 (m+1)⁺.

40

¹H NMR (CDCl₃): 0.3-0.55 (m, 4H); 1.15-1.3 (m, 1H); 1.8-1.9 (m, 1H); 2.2-2.4 (m, 3H); 2.55-2.85 (m, 3H); 3.2-3.3 (m, 1H); 7.1-7.5 (m, 3H), 9.65 (s, 1H) ppm.

45

4(c) 3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-morpholinosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)glutarimide

50

[0065] This was made in the same way as described in Example 1(f) above using the chiral aldehyde of Example 4(b) above and 3-(4-morpholinosulphonylpiperazin-1-yl)azetidine bis trifluoroacetate (Preparation 3).

LRMS m/z = 628 (m+1)⁺.

Found : C 52.8%; H 6.02%; N 11.01%. C₂₈H₃₉Cl₂N₅O₅S.0.5H₂O requires C52.74%; H 6.34%; N 10.99%.

55

¹H NMR (CDCl₃): 0.3-0.6 (m, 3H); 1.1-1.25 (m, 2H); 1.8-1.95 (m, 1H); 2.0-2.1 (m, 1H); 2.15-2.45 (m, 8H); 2.5-2.75 (m, 2H); 2.75-2.8 (m, 2H); 2.9-3.0 (m, 1H); 3.2-3.4 (m, 8H); 3.4-3.45 (m, 2H); 3.65-3.8 (m, 6H); 7.05-7.1 (m, 1H); 7.3-7.35 (m, 1H); 7.4-7.45 (m, 1H) ppm.

60

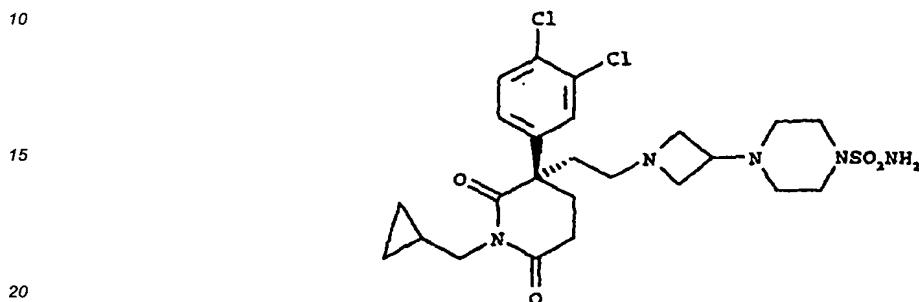
[0066] Examples 5-7 were made in the same way as described in Example 4(c) above, using the appropriate amine or amine salt (see Preparations).

55

EXAMPLE 5:

5 3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclopropylmethyl-3-(3,4-dichlorophenyl)glutarimide

[0067]

LRMS m/z = 558 (m)⁺.Found : C 51.09%; H 5.62%; N 11.87 %. C₂₄H₃₃Cl₂N₅O₄S. 0.5H₂O requires C

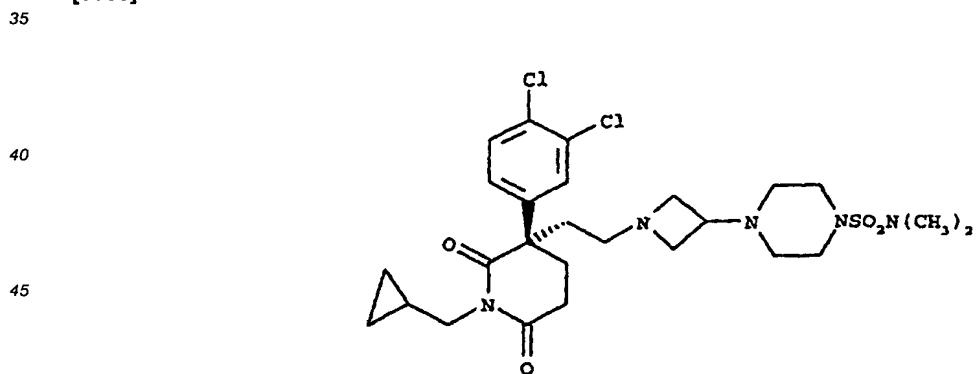
25 50.79%; H 6.05%; N 12.34%.

1H NMR (CDCl₃): 0.3-0.6 (m, 4H); 1.1-1.3 (m, 1H); 1.8-2.0 (m, 1H); 2.0-2.1 (m, 1H); 2.2-2.4 (m, 8H); 2.4-2.55 (m, 1H); 2.8-3.05 (m, 4H); 3.2-3.4 (m, 6H); 3.6-3.9 (m, 2H); 4.2-4.4 (m, 2H); 7.0-7.05 (m, 1H); 7.35-7.45 (m, 2H) ppm.

EXAMPLE 6:

30 3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-dimethylaminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)glutarimide

[0068]

50 LRMS m/z = 586 (m)⁺.Found : C 52.43%; H 6.44%; N 11.75 %. C₂₆H₃₇Cl₂N₅OS. 0.5H₂O requires C

52.14%; H 6.07%; N 11.53%.

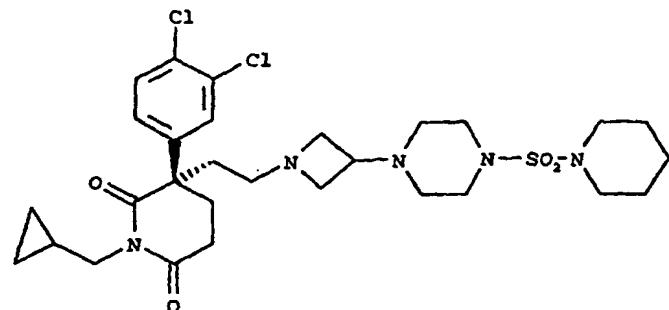
1H NMR (CDCl₃): 0.3-0.6 (m, 4H); 1.1-1.2 (m, 1H); 1.6-1.8 (m, 2H); 1.8-1.95 (m, 1H); 2.0-2.2 (m, 1H); 2.2-2.4 (m, 8H); 2.5-2.8 (m, 2H); 2.8-3.0 (m, 7H); 3.2-3.4 (m, 4H); 3.4-3.6 (m, 2H); 3.7-3.9 (m, 2H); 7.05-7.15 (m, 1H); 7.3-7.5 (m, 2H) ppm.

EXAMPLE 7:

5 3(S)-1-Cyclopropylmethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-piperidinosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)glutarimide

[0069]

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LRMS m/z = 626 (m)⁺.Found : C 64.62%; H 6.72%; N 10.98 %. C₂₉H₄₁Cl₂N₅O₄S. 0.5H₂O requires C 54.79%; H 6.67%; N 11.02%.25 ¹H NMR (CDCl₃): 0.3-0.6 (m, 4H); 1.1-1.2 (m, 1H); 1.8-1.95 (m, 1H); 2.1-2.5 (m, 11H); 2.5-2.7 (m, 3H); 2.8-3.0 (m, 3H); 3.2-3.4 (m, 11H); 3.4-3.6 (m, 2H); 3.6-3.85 (m, 2H); 7.05-7.1 (m, 1H); 7.3-7.5 (m, 2H) ppm.EXAMPLE 8:

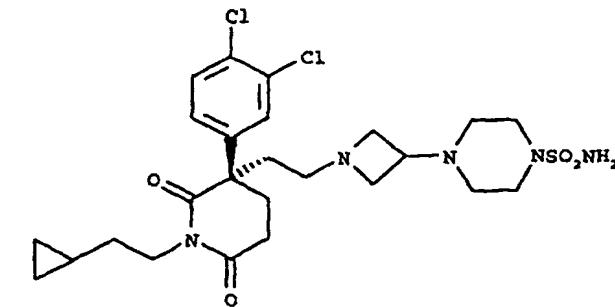
30 3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclopropylethyl-3-(3,4-dichlorophenyl)glutarimide

[0070]

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50 8(a) 3(S)-3-Allyl-1-cyclopropylethyl-3-(3,4-dichlorophenyl)-glutarimide

[0071] This was made by the same method as described in Example 1(d) above, using the compound of Example 2(b) and 2-methanesulphonyloxyethylcyclopropane (Preparation 5).

LRMS m/z = 366 (m+1)⁺.55 ¹H NMR (CDCl₃): 0.0-0.1 (m, 2H); 0.4-0.45 (m, 2H); 0.6-0.7 (m, 1H); 0.8-0.9 (m, 2H); 2.1-2.8 (m, 6H); 3.9-3.95 (m, 2H); 5.1-5.15 (m, 2H); 5.5-5.65 (m, 1H); 7.1-7.4 (m, 3H) ppm.

8(b) 3(S)-1-(2-cyclopropylethyl)-3-(3,4-dichlorophenyl)-3-formylmethylglutarimide

[0072] This was made by the same method as described above in Example 1(e), using the compound of Example 8(a).

5 LRMS m/z = 368 (m+1)⁺.

¹H NMR (CDCl₃): 0.05-0.15 (m, 2H); 0.4-0.45 (m, 2H); 0.65-0.75 (m, 1H); 1.45-1.55 (m, 2H); 2.1-2.45 (m, 3H); 2.55-2.65 (m, 2H); 2.8-2.9 (m, 1H); 3.9-4.05 (m, 2H); 7.05-7.45 (m, 3H); 9.65 (s, 1H) ppm.

10 8(c) 3(S)-3-(2-(3-(4-Aminosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)-1-cyclopropylethyl-3-(3,4-dichlorophenyl)glutarimide

[0073] This was made by the same method as described above in Example 1(f), using the compound of Example 8(b) and 3-(4-aminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate (Preparation 2).

LRMS m/z = 547 (m+1)⁺.

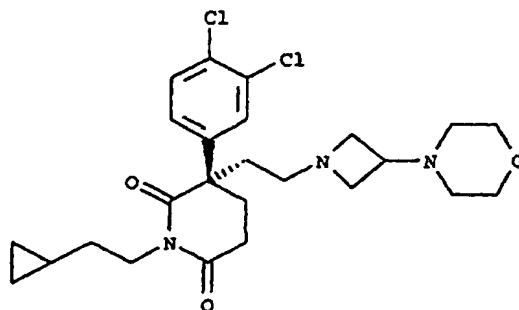
15 Found : C 51.22%; H 5.78%; N 11.49 %. C₂₅H₃₅Cl₂N₅O₄S. 0.25 CH₂Cl₂ requires C 51.17%; H 6.04%; N 11.32%.

¹H NMR (CDCl₃): 0.0-0.1 (m, 2H); 0.3-0.45 (m, 2H); 0.6-0.7 (m, 1H); 1.4-1.55 (m, 2H); 1.8-1.9 (m, 1H); 1.9-2.0 (m, 1H); 2.1-2.6 (m, 10H); 2.7-2.8 (m, 2H); 2.85-2.95 (m, 1H); 3.1-3.3 (m, 4H); 3.4-3.55 (m, 2H); 3.8-4.0 (m, 2H); 4.4-4.6 (m, 2H); 7.0-7.05 (m, 1H); 7.2-7.3 (m, 1H); 7.3-7.4 (m, 1H) ppm.

20 EXAMPLE 9:

3(S)-1-Cyclopropylethyl-3-(3,4-dichlorophenyl)-3-(2-(3-(4-morpholinosulphonylpiperazin-1-yl)azetidin-1-yl)ethyl)glutarimide

25 **[0074]**



[0075] This was made by the same method as described above in Example 1 (f), using the aldehyde of Example 8(b) and 3-morpholinoazetidine dihydrochloride (Preparation 1).

LRMS m/z = 494 (m)⁺.

45 Found : C 57.08%; H 6.52%; N 7.83%. C₂₅H₃₃Cl₂N₃O₂. 0.5 CH₂Cl₂ requires C 57.04%; H 6.38%; N 7.83%.

¹H NMR (CDCl₃): 0.0-0.1 (m, 2H); 0.4-0.6 (m, 2H); 0.6-0.8 (m, 1H); 1.3-1.5 (m, 2H); 1.8-1.95 (m, 1H); 1.95-2.05 (m, 1H); 2.1-2.75 (m, 9H); 2.8-3.0 (m, 4H); 3.4-3.5 (m, 2H); 3.6-3.75 (m, 4H); 3.8-4.0 (m, 2H); 7.0-7.05 (m, 1H); 7.25-7.4 (m, 2H) ppm.

50 [0076] The following Preparations illustrate the synthesis of certain starting materials used in the preceding Examples.

PREPARATIONS

PREPARATION 1, 3-Morpholinoazetidine dihydrochloride 1(a) 1-Diphenylmethylazetidin-3-ol

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[0077] A solution of benzhydrylamine (200ml, 1,16mol) and epichlorohydrin (186ml, 1 mol equiv) in methanol (600ml) was stirred at room temperature for 5 days and then heated to 40°C for 2 days. The solvent was then removed *in vacuo*, the residue dissolved in isopropyl alcohol (500ml) and the solution heated under reflux for 6 hours. The solution

was cooled to room temperature and the precipitate filtered off. The solid was partitioned between dichloromethane (400ml) and saturated NaHCO_3 solution (500ml). The aqueous phase was extracted with dichloromethane (2x400ml) and the combined organic phases dried over anhydrous MgSO_4 . The solvent was then removed *in vacuo* to give the title compound (86g) as a crystalline solid.

5 ^1H NMR (CDCl_3): 1.8-2.3 (s,br,1H); 2.85-2.9 (m,2H); 3.5-3.55 (m,2H); 4.35 (s,1H); 4.4-4.5 (m,1H); 7.15-7.4 (m, 10H) ppm.

1(b) 1-Diphenylmethyl-3-methanesulphonyloxyazetidine

10 [0078] To a solution of the compound from Preparation 1(a) (65.9g, 275.7 mmol) in dry dichloromethane (700ml) at 0°C under nitrogen was added triethylamine (57ml, 1.5 mol eq). After 5 minutes, methanesulphonyl chloride (25.6ml, 1.2 mol equiv) was added and the mixture stirred for 1 hour. Water (300ml) was then added and the mixture extracted with dichloromethane (3x300ml). The combined organic layers were dried over MgSO_4 , and the solvent was then removed *in vacuo*. The residue was chromatographed using silica gel eluting with methanol:dichloromethane (1:49) to give the title compound (73.4g) as a solid. ^1H NMR (CDCl_3): 2.95 (s,3H); 3.15-3.25 (m, 2H); 3.6-3.65 (m, 2H); 4.4 (s,1H); 5.05-5.15 (m,1H); 7.15-7.4 (m,10H) ppm.

1(c) 1-Diphenylmethyl-3-morpholinoazetidine

20 [0079] A solution of 1-diphenylmethyl-3-methanesulphonyloxyazetidine (Preparation 1(b)) (24.46g, 7.72mmol), potassium carbonate (32g, 3 mol equiv) and morpholine (7.34ml, 1.09 mol equiv) in acetonitrile (200ml) was heated under reflux for 4 hours. The solution was then cooled to room temperature, water (50ml) added and the mixture concentrated *in vacuo*. The residue was then partitioned between ethyl acetate (400ml) and water (400ml) and the organic phase washed with water (2x400ml). The organic phase was dried over MgSO_4 , and the solvent removed *in vacuo*. The residue was chromatographed using silica gel eluting with hexane : diethyl ether (1:1) to give the title compound (16.5g). ^1H NMR (CDCl_3): 2.25-2.3 (m,4H); 2.85-3.05 (m,3H); 3.35-3.4 (m,2H); 3.7-3.75 (m,4H); 4.45 (s,1H); 7.15-7.45 (m,10H) ppm.

1(d) 3-Morpholinoazetidine dihydrochloride

30 [0080] A mixture of 1-diphenylmethyl-3-morpholinoazetidine (Preparation 1(c)) (18.6g, 60.4mmol), palladium hydroxide (2g), ethanol (200ml) and 1N aqueous HCl (52ml) was stirred under an atmosphere of hydrogen at 345kPa (50p. s.i.) for 3 days. The catalyst was then removed by filtration and the filtrate evaporated to dryness. Addition of dichloromethane (100ml) to the residue and trituration gave a solid which was recrystallised from methanol to give the title compound (10.2g) as a crystalline solid. LRMS m/z = 179 (m+1)⁺.

PREPARATION 2. 3-(4-Aminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

2(a) 1-(t-Butoxycarbonyl)-3-(piperazin-1-yl)azetidine methanesulphonate

40 [0081] Piperazine (149.2g, 8 mol equiv) was heated to a melt and 1-(t-butoxycarbonyl)-3-methanesulphonyloxyazetidine (see (International Patent Application Publication No. WO93/19059) (54.5g, 217mmol) was then added. The mixture was heated at 115°C for 24 hours, then cooled and the excess piperazine removed *in vacuo*. The residue was purified by flash chromatography (silica, methanol:dichloromethane, 1:19) to give the title compound (51g). LRMS m/z = 242 (m+1)⁺.

^1H NMR (CDCl_3): 1.4 (m,9H); 2.5-2.6 (m,4H); 3.1-3.25 (m,5H); 3.7-3.8 (m,2H); 3.9-3.95 (m,2H); 4.6 (br, s, 1H) ppm.

2(b) 3-(4-Aminosulphonylpiperazin-1-yl)-1-(t-butoxycarbonyl)azetidine

50 [0082] A solution of the compound of Preparation 2(a) (50g, 132.6mmol) and sulphamide (88g, 6.9 mol equiv) in 1,4-dioxane (1300ml) was heated under reflux for 55 hours. The solution was cooled and the solvent removed *in vacuo*. The residue was purified by flash chromatography (silica, methanol:dichloromethane, 1:19) to give the title compound (50g).

55 ^1H NMR (CDCl_3): 1.45 (s,9H); 2.4-2.5 (m,4H); 3.1-3.2 (m, 1H); 3.25-3.3 (m,4H); 3.75-3.8 (m,2H); 3.85-3.9 (m,2H); 4.3 (br, s, 2H) ppm.

2(c) 3-(4-Aminosulphonylpiperazin-1-yl)azetidine bistrifluoroacetate

[0083] To a solution of the compound of Preparation 2(b) (364mg, 1.14 mmol) in dichloromethane (6ml) under nitrogen at 0°C was slowly added trifluoroacetic acid (3ml, 35 mol equiv) and the reaction mixture was allowed to warm to room temperature over 2 hours. The solvent was then removed *in vacuo* and the residue azeotroped with dichloromethane (3x10ml). The resulting oil was triturated with diethyl ether to give the title compound (379mg) which was used without further purification.

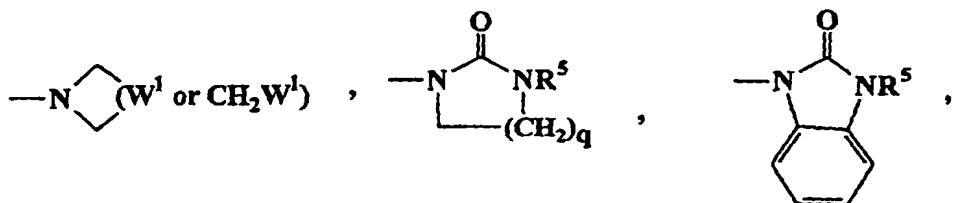
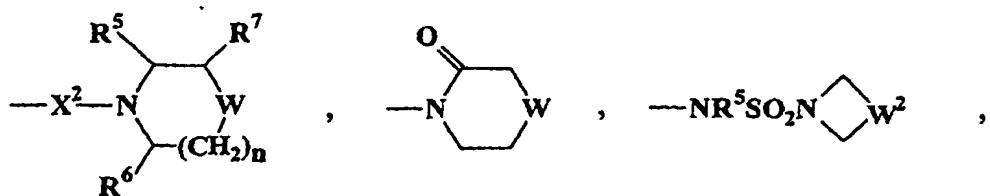
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or a pharmaceutically acceptable salt thereof, wherein

5 R is C₃-C₇ cycloalkyl, aryl or C₁-C₆ alkyl, said C₁-C₆ alkyl being optionally substituted by fluoro, -COOH, -COO(C₁-C₄) alkyl, C₃-C₇ cycloalkyl, adamantyl, aryl or het¹, and said C₃-C₇ cycloalkyl being optionally substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, C₃-C₇ cycloalkyl, C₁-C₄ alkoxy, hydroxy, fluoro, fluoro(C₁-C₄) alkyl and fluoro(C₁-C₄)alkoxy;

R¹ is phenyl, benzyl, naphthyl, thienyl, benzothienyl or indolyl, each optionally substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo and trifluoromethyl;

10 R² is -CO₂H, -CONR³R⁴, -CONR⁵(C₃-C₇ cycloalkyl), -NR⁵(C₂-C₅ alkanoyl), -NR³R⁴, -NR⁵CONR⁵R⁶, (C₃-C₇ cycloalkyl-C₁-C₄ alkyl)R⁵N-, (C₃-C₇ cycloalkyl-C₁-C₄ alkyl)₂N, -NR⁵COCF₃, -NR⁵SO₂CF₃, -NR⁵(SO₂C₁-C₄ alkyl), -NR⁵SO₂NR⁵R⁶, -NR⁵(SO₂ aryl), -N(aryl)(SO₂C₁-C₄ alkyl), -OR⁵, -O(C₃-C₇ cycloalkyl), -SO₂NR⁵R⁶, het³ or a group of the formula:-



R³ and R⁴ are each independently selected from H and C₁-C₄ alkyl optionally substituted by hydroxy, C₁-C₄ alkoxy, -S(O)_p(C₁-C₄ alkyl), amino, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂ or het²;

45 R⁵ and R⁶ are each independently selected from H, C₁-C₄ alkyl and C₃-C₇ cycloalkyl-C₁-C₄ alkyl, said C₁-C₄ alkyl and C₃-C₇ cycloalkyl-C₁-C₄ alkyl being optionally substituted by fluoro;

R⁷ is H, C₁-C₄ alkyl, hydroxy, fluoro(C₁-C₄)alkyl or phenyl, said phenyl being optionally substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, fluoro(C₁-C₄)alkyl, halo, C₁-C₄ alkoxy and fluoro(C₁-C₄) alkoxy;

R⁸ is H, fluoro, hydroxy, C₁-C₄ alkoxy, C₂-C₅ alkanoyl or C₂-C₅ alkanoyloxy;

50 R⁹ is -NR⁵R⁶, -NR⁵COR⁵, -NR⁵SO₂CF₃, -NR⁵(SO₂C₁-C₄ alkyl), -NR⁵SO₂NR⁵R⁶, -NR⁵COO(C₁-C₄ alkyl), -NR⁵CONR⁵R⁶, -NR⁵(SO₂morpholino), -NR⁵(SO₂ aryl), -N(aryl)(SO₂C₁-C₄ alkyl) or a group of the formula:



5

X is C₁-C₄ alkylene;

10 X¹ is a direct link or C₁-C₆ alkylene;

X² is a direct link, CO, SO₂ or NR⁵CO where the carbonyl is attached to the ring nitrogen atom;

W is methylene, CO, CH(OH), C(OH)₂, CH(C₁-C₄ alkoxy), CHCO₂H, CHCO₂(C₁-C₄ alkyl), CHCONR⁵R⁶, CHF, CF₂, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino), CH(benzoxazol-2-yl), CHR⁹, O, S(O)_p, NR⁵, N(C₃-C₇ cycloalkyl), NSO₂(C₁-C₄ alkyl), NSO₂NR⁵R⁶, NSO₂CF₃, NSO₂(morpholino), NSO₂(aryl),

15



20

NCONR⁵R⁶, NCOR⁵, NCO(aryl) or NCO₂(C₁-C₄ alkyl);

W¹ is methylene, CO, CH(OH), C(OH)₂, CH(C₁-C₄ alkoxy), CHCO₂H, CHCO₂(C₁-C₄ alkyl), CHCONR⁵R⁶, CHF, CF₂, CH(azetidin-1-yl), CH(pyrrolidin-1-yl), CH(piperidin-1-yl), CH(morpholino) or CHR⁹.

W² is W¹, -CH₂W¹-, -CH₂WCH₂- or -CH₂CH₂WCH₂-;

25 n is 1 or 2 when W is other than methylene and is 0, 1 or 2 when W is methylene;

n is 0, 1 or 2;

p is 0, 1 or
q is 1 or 2.

q is 1 or 2,
r is 1, 2, 3 or

FIG 1, 2, 3 or 4;
"and" used in t

³⁰ "aryl", used in the definition of R, R₂, R₃ and W, means naphthyl or phenyl, each optionally substituted by C₁-C₄ alkyl, halo, -OR⁵, fluoro(C₁-C₄)alkyl, C₂-C₅ alkanoyl, -CONR⁵R⁶, -SO₂NR⁵R⁶ or phenyl;

"het", used in the definition of R, means thiienyl or a 5- or 6- membered ring heteroaryl group containing either 1 or 2 nitrogen heteroatoms or one nitrogen heteroatom and one oxygen or sulphur heteroatom, each optionally substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, fluoro(C₁-C₄ alkyl) and fluoro(C₁-C₄ alkoxy);

35 "het²", used in the definitions of R³ and R⁴, means a 4- to 7- membered ring, non-aromatic, heterocyclic group containing 1 or 2 heteroatoms each independently selected from nitrogen, oxygen and S(O)_p, said group being optionally C-substituted by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy and fluoro(C₁-C₄)alkyl, and said ring nitrogen heteroatom optionally bearing a H, C₁-C₄ alkyl, C₂-C₅ alkanoyl, -CONR⁵R⁶ or -SO₂NR⁵R⁶ substituent;

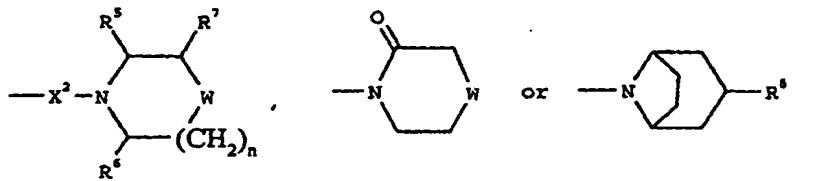
40 and "het³", used in the definition of R², means an optionally benzo-fused, N-linked, 5-membered ring heteroaryl group containing from 1 to 4 nitrogen heteroatoms, which het³ is optionally substituted, including in the benzo-fused portion, by 1 or 2 substituents each independently selected from C₁-C₄ alkyl, fluoro and fluoro(C₁-C₄)alkyl.

45 2. A compound or salt according to claim 1 wherein R is aryl, optionally substituted C₃-C₇ cycloalkyl, or is C₁-C₆ alkyl substituted by aryl or optionally substituted C₃-C₇ cycloalkyl.

3. A compound or salt according to any one of the previous claims wherein R¹ is phenyl optionally substituted by 1 or 2 halo substituents.

50 4. A compound or salt according to any one of the previous claims wherein R² is -CONR³R⁴, -CONR⁵(C₃-C₇ cycloalkyl), -NR³R⁴, het³ or a group of the formula:-

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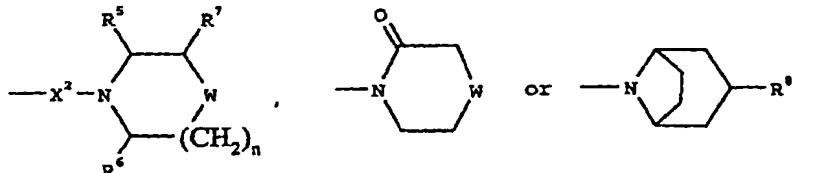
where R^3 and R^4 are each independently selected from C_1-C_4 alkyl and C_1-C_4 alkyl substituted by hydroxy or C_1-C_4 alkoxy, R^5 and R^6 are each independently selected from H, C_1-C_4 alkyl optionally substituted by fluoro and C_3-C_7 cycloalkyl- C_1-C_4 alkyl, R^7 is H, hydroxy or phenyl, R^8 is hydroxy or C_2-C_5 alkanoyloxy, W is methylene, $CH(OH)$, CHF , CO, $CH(C_1-C_4)$ alkoxy, $CHCO_2H$, $CHCO_2(C_1-C_4)$ alkyl, $CH(benzoxazol-2-yl)$, $CHNR^5R^6$, $CHNR^5COR^5$, $CHNR^5(SO_2C_1-C_4)$ alkyl, $CHNR^5COO(C_1-C_4)$ alkyl, O, $S(O)_p$, $NR^5, NSO_2(C_1-C_4)$ alkyl, $NSO_2NR^5R^6$, NSO_2 (morpholino), NSO_2 (piperidino), $NCONR^5R^6$, $NCOR^5$, NCO (aryl) or $NCO_2(C_1-C_4)$ alkyl, n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, or 2.

20

5. A compound or salt according to any one of the previous claims wherein X is ethylene or propylene.
6. A compound or salt according to any one of the previous claims wherein X^1 is a direct link.
7. A compound or salt according to any one of the previous claims wherein R is optionally substituted C_3-C_7 cycloalkyl or C_1-C_6 alkyl substituted by optionally substituted C_3-C_7 cycloalkyl.

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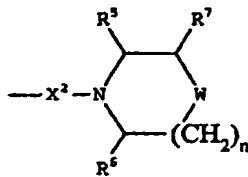
8. A compound or salt according to any one of the previous claims wherein R^1 is phenyl optionally substituted by 1 or 2 substituents each independently selected from fluoro and chloro.
9. A compound or salt according to any one of the previous claims wherein R^2 is $-CONR^3R^4$, $-CONR^5(C_3-C_7)$ cycloalkyl, $-NR^3R^4$, a N-linked, 5-membered ring heteroaryl group containing 1 or 2 nitrogen heteroatoms, or a group of the formula:-



where R^3 and R^4 are each independently selected from methyl and C_1-C_4 alkyl substituted by hydroxy or methoxy, R^5 and R^6 are each independently selected from H, methyl, trifluoromethyl and cyclopropylmethyl, R^7 is H, hydroxy or phenyl, R^8 is hydroxy or acetoxy, W is methylene, $CH(OH)$, $CHOCH_3$, CHF , CO, $CHOCH_2CH_3$, $CHO(CH_2)_2CH_3$, $CHOC(CH_3)_3$, $CHCO_2H$, $CHCO_2CH_3$, $CHCO_2CH_2CH_3$, $CH(benzoxazol-2-yl)$, $CHNH_2$, $CHNHCH_2$ (cyclopropyl), $CHNHCOCH_3$, $CHNHSO_2CH_3$, $CHNHCO_2C(CH_3)_3$, O, $S(O)_p$, NH, NCH_3 , NCH_2 (cyclopropyl), NSO_2CH_3 , NSO_2NH_2 , NSO_2NHCH_3 , $NSO_2N(CH_3)_2$, NSO_2 (morpholino), NSO_2 (piperidino), $NCONH_2$, $NCONHCH_3$, $NCOCH_3$, $NCOCF_3$, NCO (phenyl) or $NCO_2C(CH_3)_3$, n is 1 or 2 when W is other than methylene and is 0 or 1 when W is methylene, and p is 0, 1 or 2.

50

10. A compound or salt according to claim 9 wherein R^2 is a group of the formula :-



10

where R^5 , R^6 , R^7 , W and n are as defined in claim 9, and X^2 is a direct link.

11. A compound or salt according to any one of the previous claims wherein R is 2-cyclopropylethyl, cyclohexyl, 4,4-difluorocyclohexyl, cyclohexylmethyl or cyclopropylmethyl.

15. 12. A compound or salt according to any one of the previous claims wherein R^1 is phenyl, 3,4-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl or 3,4-dichlorophenyl.

20. 13. A compound or salt according to any one of claims 1 to 9 or claim 11 or 12, wherein R^2 is N-(2-methoxyethyl)-N-methylcarbamoyl, N-cyclohexylcarbamoyl, N-(2-hydroxyethyl)-N-methylamino, N-(2-hydroxy-2-methylpropyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, imidazol-1-yl, 3-hydroxypyrrolidin-1-yl, piperidin-1-yl, 2,6-dimethylpiperidin-1-yl, 3-hydroxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, 4-methoxypiperidin-1-yl, 4-ethoxypiperidin-1-yl, 4-(n-propoxy)piperidin-1-yl, 4-(t-butoxy)piperidin-1-yl, 4-carboxypiperidin-1-yl, 4-methoxycarbonylpiperidin-1-yl, 4-ethoxycarbonylpiperidin-1-yl, 4-(benzoxazol-2-yl)piperidin-1-yl, 4-aminopiperidin-1-yl, 4-cyclopropylmethylaminopiperidin-1-yl, 4-acetamidopiperidin-1-yl, 4-methanesulphonamidopiperidin-1-yl, 4-(t-butoxycarbonylamino)piperidin-1-yl, morpholino, 2-phenylmorpholino, homomorpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-cyclopropylmethylpiperazin-1-yl, 4-methanesulphonylpiperazin-1-yl, 4-aminosulphonylpiperazin-1-yl, 4-methylaminosulphonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl, 4-carbamoylpiperazin-1-yl, 4-N-methylcarbamoylpiperazin-1-yl, 4-acetyl piperazin-1-yl, 4-trifluoroacetyl piperazin-1-yl, 4-benzoylpiperazin-1-yl, 4-(t-butoxycarbonyl)piperazin-1-yl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, 3-oxomorpholino, 3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl, 3-acetoxy-8-azabicyclo[3.2.1]oct-8-yl, 4-fluoropiperidin-1-yl or 4-oxopiperidin-1-yl.

35. 14. A compound or salt according to any one of the previous claims wherein R^1 is 3,4-dichlorophenyl.

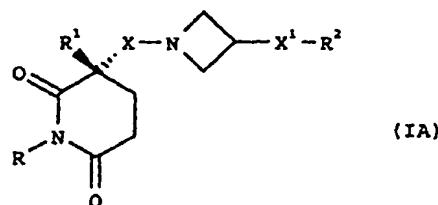
40. 15. A compound or salt according to any one of the previous claims wherein R^2 is 4-aminopiperidin-1-yl, 4-carboxypiperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholino, 1-oxothiomorpholino, 4-aminosulphonylpiperazin-1-yl, 4-methanesulphonylpiperazin-1-yl, 4-dimethylaminosulphonylpiperazin-1-yl, 4-morpholinosulphonylpiperazin-1-yl, 4-piperidinosulphonylpiperazin-1-yl, 4-fluoropiperidin-1-yl or 4-oxopiperidin-1-yl.

45. 16. A compound or salt according to any one of the previous claims wherein

- (i) R is cyclohexylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is morpholino;
- (ii) R is cyclohexylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl;
- (iii) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-morpholinosulphonylpiperazin-1-yl;
- (iv) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl;
- (v) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-dimethylaminosulphonylpiperazin-1-yl;
- (vi) R is cyclopropylmethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-piperidinosulphonylpiperazin-7-yl;
- (vii) R is cyclopropylethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is 4-aminosulphonylpiperazin-1-yl; or
- (viii) R is cyclopropylethyl, R^1 is 3,4-dichlorophenyl, X is ethylene, X^1 is a direct link and R^2 is morpholino.

17. A compound or salt according to any one of the previous claims wherein the compound of formula (I) has the stereochemistry shown below in formula (IA) at the position of attachment of the X and R¹ groups to the glutarimide ring:

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18. A pharmaceutical composition comprising a compound or salt according to any one of the previous claims and a pharmaceutically acceptable diluent or carrier.

20

19. A compound or salt according to any one of claims 1 to 17, or composition thereof according to claim 18, for use as a medicament.

25

20. The use of a compound or salt according to any one of claims 1 to 17, or composition thereof according to claim 18, for the manufacture of a medicament for the treatment of a disease by producing an antagonist effect on a tachykinin acting at the human neurokinin-1 (NK₁), human neurokinin-2 (NK₂) or human neurokinin-3 (NK₃) receptor, or a combination of two or more thereof.

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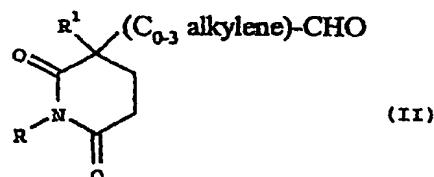
21. The use as in claim 20 where the disease is an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastro-intestinal (GI) disorder such as functional bowel disease, irritable bowel syndrome, gastro-oesophageal reflux, faecal incontinence, colitis or Crohn's disease, a urogenital tract disorder such as incontinence, hyperreflexia or cystitis, a pulmonary disorder such as chronic obstructive airways disease, an allergy such as eczema, contact dermatitis or rhinitis, a hypersensitivity disorder such as to poison ivy, a peripheral neuropathy such as diabetic neuropathy, neuralgia, causalgia, painful neuropathy, a bum, herpetic neuralgia or post-herpetic neuralgia, cough or acute or chronic pain.

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22. A compound

(a) of formula (II)

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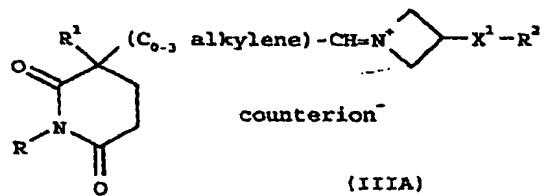


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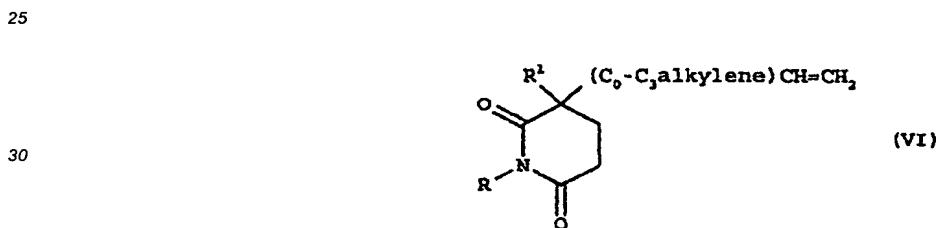
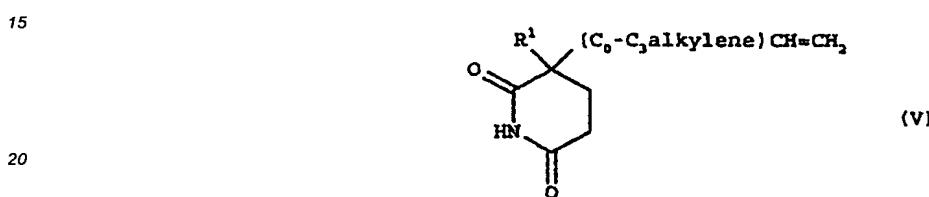
where R and R¹ are as previously defined in Claim 1;

(b) of the formula (IIIA)

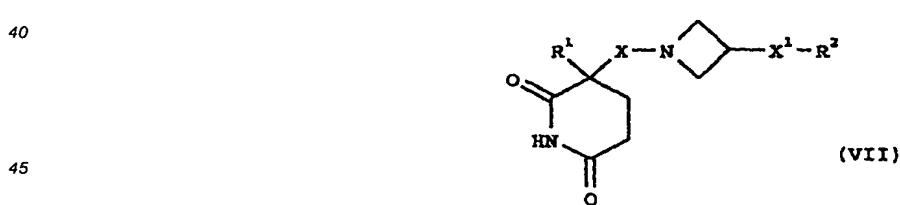
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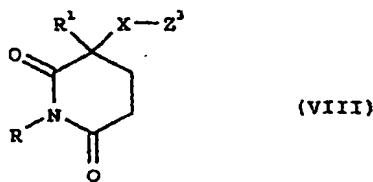
10 where R, R¹, X¹ and R² are as previously defined in Claim 1, and the counterion is hydroxide or acetate;
 (c) of formula (V) or (VI)



35 where R and R¹ are as previously defined in Claim 1;
 (d) of the formula (VII)



50 where X, X¹, R¹ and R² are as previously defined in Claim 1;
 (e) of the formula (VIII)

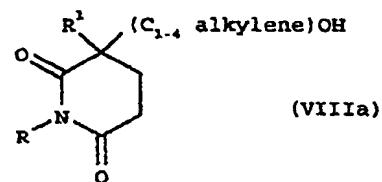


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where X, R and R¹ are as previously defined for a compound of the formula (I) and Z³ is a suitable leaving group, e.g. chloro, bromo, iodo, methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy;

(f) of the formula (VIIIa)

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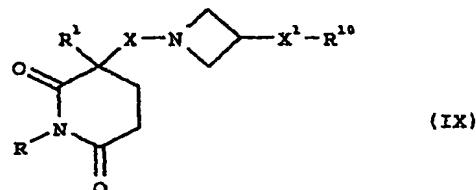


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where R and R¹ are as defined in Claim 1;

(g) of a compound of the formula (IX)

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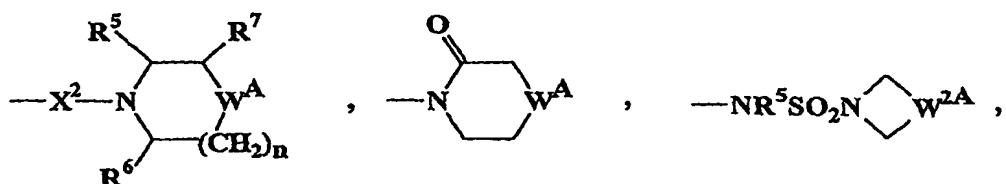


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where R, R¹, X and X¹ are as defined in Claim 1 and R¹⁰ is a group of the formula:



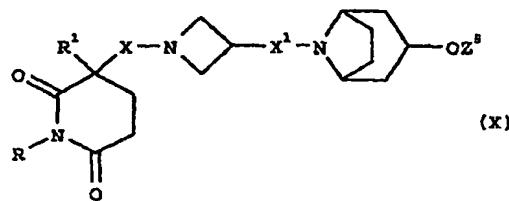
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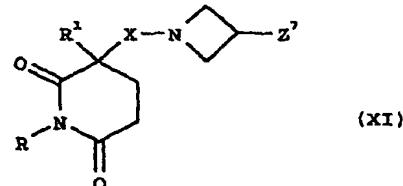
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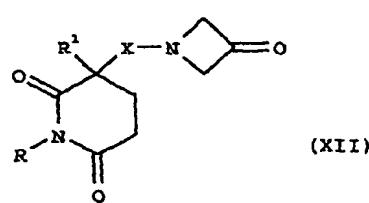
10 , respectively, R^9A is $-NZ^4R^5$, W^A is NZ^4 or $CHNZ^4R^5$, W^1A is $CHNZ^4R^5$, W^2A is W^1A , $-CH_2W^1A$, $-CH_2W^A$, CH_2- or $-CH_2CH_2W^A$, X , X^1 , X^2 , R , A , R^1 , R^4 , R^5 , R^6 , R^7 , m and n are as previously defined in Claim 1 and Z^4 is a suitable protecting group, e.g. t-butoxycarbonyl (e.g. a compound of the formula (I) where W is $NCO_2C(CH_3)_3$ or R^9 is $-NR^5CO_2C(CH_3)_3$) or benzyloxycarbonyl; (h) of the formula (X)



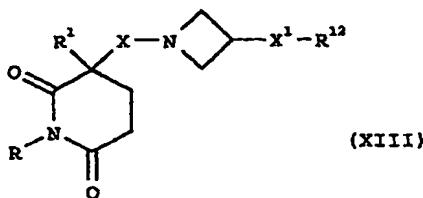
20 25 where Z^5 is a suitable protecting group, e.g. acetyl or tetrahydropyran-2-yl, and X , X^1 , R and R^1 are as previously defined in Claim 1; (i) of a compound of the formula (XI)



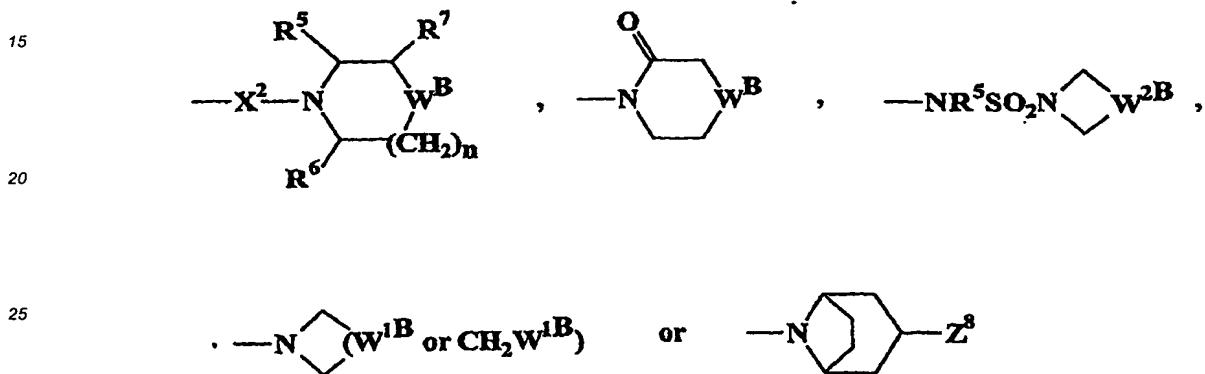
35 40 where X , R and R^1 are as previously defined for a compound of the formula (I) and Z^7 is a suitable leaving group, e.g. methanesulphonyloxy or p-toluenesulphonyloxy; (j) of the formula (XII)



50 55 where X , R and R^1 are as previously defined in Claim 1; or (k) of the formula (XIII):



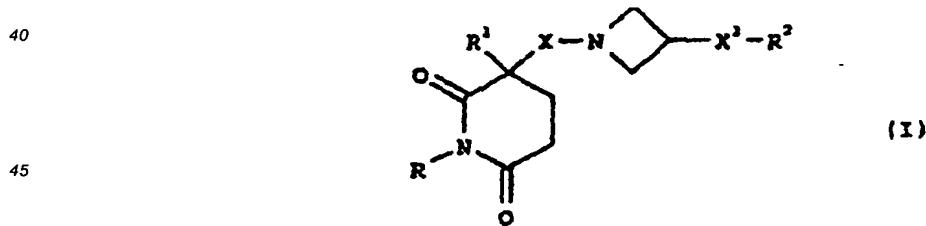
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wherein R¹² is

wherein W^B and W^{1B} are CHZ⁸, W^{2B} is W^{1B}, -CH₂W^{1B}-, -CH₂W^BCH₂- or -CH₂CH₂W^BCH₂-, Z⁸ is a suitable leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or p-toluenesulphonyloxy, and X, X¹, X², R, R¹, R⁵, R⁶, R⁷ and n are as previously defined in Claim 1.

35 Patentansprüche

1. Verbindung der Formel (I):



50 oder ein pharmazeutisch verträgliches Salz davon, worin

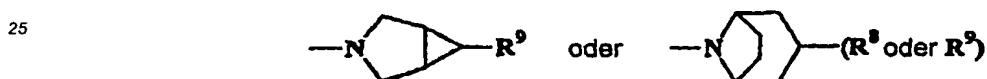
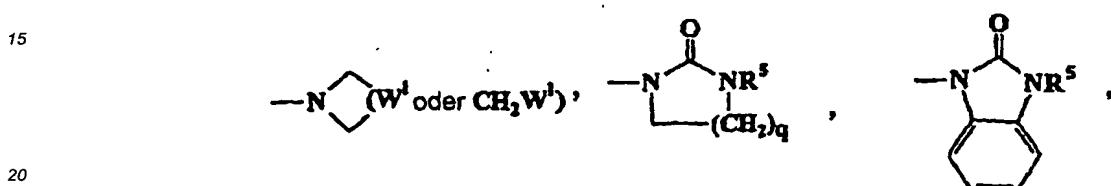
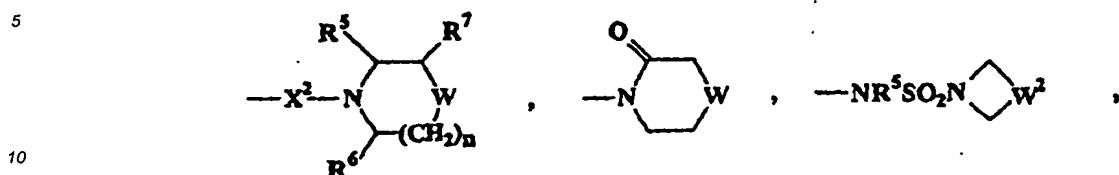
R C₃-C₇-Cycloalkyl, Aryl oder C₁-C₆-Alkyl darstellt, wobei das C₁-C₆-Alkyl gegebenenfalls mit Fluor, -COOH, -COO(C₁-C₄)-Alkyl, C₃-C₇-Cycloalkyl, Adamantyl, Aryl oder het¹ substituiert ist und das C₃-C₇-Cycloalkyl gegebenenfalls mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C₁-C₄-Alkyl, C₃-C₇-Cycloalkyl, C₁-C₄-Alkoxy, Hydroxy, Fluor, Fluor-(C₁-C₄)alkyl und Fluor(C₁-C₄)alkoxy, substituiert ist;

55 R¹ Phenyl, Benzyl, Naphthyl, Thienyl, Benzothienyl oder Indolyl darstellt, jeweils gegebenenfalls substituiert mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C₁-C₄-Alkyl, C₁-C₄-Alkoxy, Halogen und Trifluormethyl;

R²-CO₂H, -CONR³R⁴, -CONR⁵(C₃-C₇-Cycloalkyl), -NR⁵(C₂-C₅-Alkanoyl), -NR³R⁴, -NR⁵CONR⁵R⁶, (C₃-C₇-Cycloalkyl-C₁-C₄-alkyl)R⁵N-, (C₃-C₇-Cycloalkyl-C₁-C₄-alkyl)₂N, -NR⁵COCF₃, -NR⁵SO₂CF₃, -NR⁵(SO₂C₁-C₄-Alkyl),

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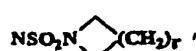
-NR⁵SO₂NR⁵R⁶, -NR⁵(SO₂-Aryl), -N(Aryl)(SO₂C₁-C₄-alkyl), -OR⁵, -O(C₃-C₇-Cycloalkyl), -SO₂NR⁵R⁶, het³ oder eine Gruppe der Formel:



30 darstellt,
 R³ und R⁴ jeweils unabhängig ausgewählt sind aus H und C₁-C₄-Alkyl, gegebenenfalls substituiert mit Hydroxy, C₁-C₄-Alkoxy, -S(O)_p(C₁-C₄-Alkyl), Amino, -NH(C₁-C₄-Alkyl), -N(C₁-C₄-Alkyl)₂ oder het²;
 R⁵ und R⁶ jeweils unabhängig aus H, C₁-C₄-Alkyl und C₃-C₇-Cycloalkyl-C₁-C₄-alkyl ausgewählt sind, wobei das C₁-C₄-Alkyl und C₃-C₇-Cycloalkyl-C₁-C₄-alkyl gegebenenfalls mit Fluor substituiert sind;
 R⁷ H, C₁-C₄-Alkyl, Hydroxy, Fluor(C₁-C₄)alkyl oder Phenyl darstellt, wobei das Phenyl gegebenenfalls mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C₁-C₄-Alkyl, Fluor(C₁-C₄)alkyl, Halogen, C₁-C₄-Alkoxy und Fluor(C₁-C₄)alkoxy, substituiert ist;
 R⁸ H, Fluor, Hydroxy, C₁-C₄-Alkoxy, C₂-C₅-Alkanoyl oder C₂-C₅-Alkanoyloxy darstellt;
 R⁹ -NR⁵R⁶, -NR⁵COR⁵, -NR⁵SO₂CF₃, -NR⁵(SO₂C₁-C₄-Alkyl), -NR⁵SO₂NR⁵R⁶, -NR⁵COO(C₁-C₄-Alkyl), -NR⁵CONR⁵R⁶, -NR⁵(SO₂-Morpholino), -NR⁵(SO₂-Aryl), -N(Aryl)(SO₂-C₁-C₄-alkyl) oder eine Gruppe der Formel:



45 darstellt;
 X C₁-C₄-Alkylen darstellt;
 X¹ eine direkte Bindung oder C₁-C₆-Alkylen darstellt;
 50 X² eine direkte Bindung, CO, SO₂ oder NR⁵CO darstellt, worin das Carbonyl an das Ringstickstoffatom gebunden ist;
 W Methylen, CO, CH(OH), C(OH)₂, CH(C₁-C₄-Alkoxy), CHCO₂H, CHCO₂(C₁-C₄-Alkyl), CHCONR⁵R⁶, CHF, CF₂, CH(Azetidin-1-yl), CH(Pyrrolidin-1-yl), CH(Piperidin-1-yl), CH(Morpholino), CH(Benzoxazol-2-yl), CHR⁹, O, S(O)_p, NR⁵, N(C₃-C₇-Cycloalkyl), NSO₂(C₁-C₄-Alkyl), NSO₂NR⁵R⁶, NSO₂CF₃, NSO₂(Morpholino), NSO₂(Aryl),



NCONR⁵R⁶, NCOR⁵, NCO(Aryl) oder NCO₂(C₁-C₄-Alkyl) darstellt;

W¹ Methylen, CO, CH(OH), C(OH)₂, CH(C₁-C₄-Alkoxy), CHCO₂H, CHCO₂(C₁-C₄-Alkyl), CHCONR⁵R⁶, CHF, CF₂, CH(Azetidin-1-yl), CH(Pyrrolidin-1-yl), CH(Piperidin-1-yl), CH(Morpholino) oder CHR⁹ darstellt;

W² W¹, -CH₂W¹-, -CH₂WCH₂- oder -CH₂CH₂WCH₂- darstellt;

5 n 1 oder 2 ist, wenn W von Methylen verschieden ist, und 0, 1 oder 2 ist, wenn W Methylen darstellt;

p 0, 1 oder 2 ist;

q 1 oder 2 ist;

r 1, 2, 3 oder 4 ist;

10 "Aryl", in der Definition von R, R², R⁹ und W verwendet, Naphthyl oder Phenyl bedeutet, jeweils gegebenenfalls substituiert mit C₁-C₄-Alkyl, Halogen, -OR⁵, Fluor(C₁-C₄)alkyl, C₂-C₅-Alkanoyl, -CONR⁵R⁶, -SO₂NR⁵R⁶ oder Phenyl;

15 "het¹", in der Definition von R verwendet, Thienyl oder eine 5- oder 6-gliedrige Ring-Heteroarylgruppe bedeutet, die entweder 1 oder 2 Stickstoff-Heteroatome oder ein Stickstoff-Heteroatom und ein Sauerstoff- oder Schwefel-Heteroatom enthält, jeweils gegebenenfalls substituiert mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C₁-C₄-Alkyl, C₁-C₄-Alkoxy, Halogen, Fluor(C₁-C₄-alkyl) und Fluor(C₁-C₄-alkoxy);

20 "het²", in den Definitionen von R³ und R⁴ verwendet, eine 4-bis 7-gliedrige, nicht-aromatische, heterocyclische Ringgruppe bedeutet, die 1 oder 2 Heteroatome enthält, jeweils unabhängig ausgewählt aus Stickstoff, Sauerstoff und S(O)_p, wobei die Gruppe gegebenenfalls mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C₁-C₄-Alkyl, C₁-C₄-Alkoxy und Fluor-(C₁-C₄)alkyl, C-substituiert ist und wobei das Ring-Stickstoffheteroatom gegebenenfalls einen Substituenten H, C₁-C₄-Alkyl, C₂-C₅-Alkanoyl, -CONR⁵R⁶ oder -SO₂NR⁵R⁶ trägt;

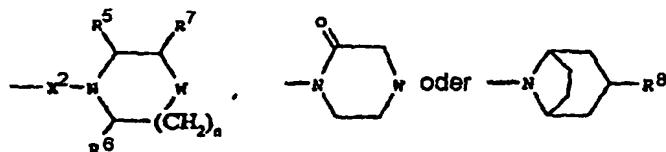
25 und "het³", in der Definition von R² verwendet, eine gegebenenfalls Benzo-kondensierte, N-gebundene, 5-gliedrige Ring-Heteroarylgruppe bedeutet, die 1 bis 4 Stickstoff-Heteroatome enthält, wobei het³ gegebenenfalls, einschließlich im Benzo-kondensierten Teil, mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus C₁-C₄-Alkyl, Fluor und Fluor(C₁-C₄)-alkyl, substituiert ist.

25 2. Verbindung oder Salz nach Anspruch 1, worin R Aryl, gegebenenfalls substituiertes C₃-C₇-Cycloalkyl darstellt oder C₁-C₆-Alkyl, substituiert mit Aryl oder gegebenenfalls substituiertem C₃-C₇-Cycloalkyl, darstellt.

30 3. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R¹ Phenyl, gegebenenfalls substituiert mit 1 oder 2 Halogensubstituenten, darstellt.

35 4. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R² -CONR³R⁴, -CONR⁵(C₃-C₇-Cycloalkyl), -NR³R⁴, het³ oder eine Gruppe der Formel:

35



40

darstellt,

45 worin R³ und R⁴ jeweils unabhängig aus C₁-C₄-Alkyl und C₁-C₄-Alkyl, substituiert mit Hydroxy oder C₁-C₄-Alkoxy, ausgewählt sind, R⁵ und R⁶ jeweils unabhängig aus H, C₁-C₄-Alkyl, gegebenenfalls substituiert mit Fluor und C₃-C₇-Cycloalkyl-C₁-C₄-alkyl, ausgewählt sind, R⁷ H, Hydroxy oder Phenyl darstellt, R⁸ Hydroxy oder C₂-C₅-Alkanoyloxy darstellt, W Methylen, CH(OH), CHF, CO, CH(C₁-C₄-Alkoxy), CHCO₂H, CHCO₂(C₁-C₄-Alkyl), CH(Benzoxazol-2-yl), CHNR⁵R⁶, CHNR⁵COR⁵, CHNR⁵(SO₂C₁-C₄-Alkyl), CHNR⁵COO(C₁-C₄-Alkyl), O, S(O)_p, NR⁵, NSO₂(C₁-C₄-Alkyl), NSO₂NR⁵R⁶, NSO₂(Morpholino), NSO₂(Piperidino), NCONR⁵R⁶, NCOR⁵, NCO(Aryl) oder NCO₂(C₁-C₄-Alkyl) darstellt, n 1 oder 2 ist, wenn W von Methylen verschieden ist, und 0 oder 1 ist, wenn W Methylen darstellt, und p 0, 1 oder 2 ist.

55

5. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin X Ethylen oder Propylen darstellt.

6. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin X¹ eine direkte Bindung darstellt.

7. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R gegebenenfalls substituiertes C₃-C₇-Cy-

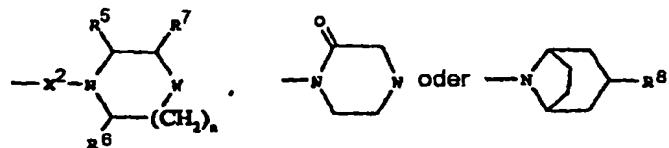
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cloalkyl oder C₁-C₆-Alkyl, substituiert mit gegebenenfalls substituiertem C₃-C₇-Cycloalkyl, darstellt.

8. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R¹ Phenyl, gegebenenfalls substituiert mit 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus Fluor und Chlor, darstellt.

5 9. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R² -CONR³R⁴, -CONR⁵(C₃-C₇-Cycloalkyl), -NR³R⁴, eine N-gebundene, 5-gliedrige Ring-Heteroarylgruppe, die 1 oder 2 Stickstoffheteroatome enthält, oder eine Gruppe der Formel:

10



15

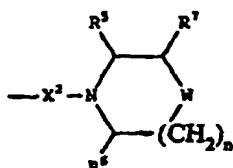
darstellt,

20 worin R³ und R⁴ jeweils unabhängig ausgewählt sind aus Methyl und C₁-C₄-Alkyl, substituiert mit Hydroxy oder Methoxy, R⁵ und R⁶ jeweils unabhängig ausgewählt sind aus H, Methyl, Trifluormethyl und Cyclopropylmethyl, R⁷ H, Hydroxy oder Phenyl darstellt, R⁸ Hydroxy oder Acetoxy darstellt, W Methylen, CH(OH), CHOCH₃, CHF, CO, CHOCH₂CH₃, CHO(CH₂)₂CH₃, CHOC(CH₃)₃, CHCO₂H, CHCO₂CH₃, CHCO₂CH₂CH₃, CH(Benzoxazol-2-yl), CHNH₂, CHNHCH₂(Cyclopropyl), CHNHCOCH₃, CHNHSO₂CH₃, CHNHCO₂C(CH₃)₃, O, S(O)_p, NH, NCH₃, NCH₂ (Cyclopropyl), NSO₂CH₃, NSO₂NH₂, NSO₂NHCH₃, NSO₂N(CH₃)₂, NSO₂(Morpholino), NSO₂(Piperidino), NCONH₂, NCONHCH₃, NCOCH₃, NCOCF₃, NCO(Phenyl) oder NCO₂C(CH₃)₃ darstellt, n 1 oder 2 ist, wenn W von Methylen verschieden ist, und 0 oder 1 ist, wenn W Methylen darstellt, und p 0, 1 oder 2 ist.

25

10. Verbindung oder Salz nach Anspruch 9, worin R² eine Gruppe der Formel:

30



35

darstellt, worin R⁵, R⁶, R⁷, W und n wie in Anspruch 9 definiert sind und X² eine direkte Bindung darstellt.

40

11. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R 2-Cyclopropylethyl, Cyclohexyl, 4,4-Difluorcylohexyl, Cyclohexylmethyl oder Cyclopropylmethyl darstellt.

45

12. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R¹ Phenyl, 3,4-Difluorphenyl, 3-Chlorphenyl, 4-Chlorphenyl oder 3,4-Dichlorphenyl darstellt.

50

13. Verbindung oder Salz nach einem der Ansprüche 1 bis 9 oder Anspruch 11 oder 12, worin R² N-(2-Methoxyethyl)-N-methylcarbamoyl, N-Cyclohexylcarbamoyl, N-(2-Hydroxyethyl)-N-methylamino, N-(2-Hydroxy-2-methylpropyl)-N-methylamino, N-(2-Methoxyethyl)-N-methylamino, Imidazol-1-yl, 3-Hydroxypyrrolidin-1-yl, Piperidin-1-yl, 2,6-Dimethylpiperidin-1-yl, 3-Hydroxypiperidin-1-yl, 4-Hydroxypiperidin-1-yl, 4-Methoxypiperidin-1-yl, 4-Ethoxypiperidin-1-yl, 4-(n-Propoxy)piperidin-1-yl, 4-(t-Butoxy)piperidin-1-yl, 4-Carboxypiperidin-1-yl, 4-Methoxycarbonylpiperidin-1-yl, 4-Ethoxycarbonylpiperidin-1-yl, 4-(Benzoxazol-2-yl)piperidin-1-yl, 4-Aminopiperidin-1-yl, 4-Cyclopropylmethylaminopiperidin-1-yl, 4-Acetamidopiperidin-1-yl, 4-Methansulfonamidopiperidin-1-yl, 4-(t-Butoxycarbonylaminoo)piperidin-1-yl, Morpholino, 2-Phenylmorpholino, Homomorpholino, Thiomorpholino, 1-Oxothiomorpholino, 1,1-Dioxothiomorpholino, Piperazin-1-yl, 4-Methylpiperazin-1-yl, 4-Cyclopropylmethylpiperazin-1-yl, 4-Methansulfonylpiperazin-1-yl, 4-Aminosulfonylpiperazin-1-yl, 4-Methylaminosulfonylpiperazin-1-yl, 4-Dimethylaminosulfonylpiperazin-1-yl, 4-Morpholinosulfonylpiperazin-1-yl, 4-Piperidinosulfonylpiperazin-1-yl, 4-Carbamoylpiperazin-1-yl, 4-N-Methylcarbamoylpiperazin-1-yl, 4-Acetyl piperazin-1-yl, 4-Trifluoracetyl piperazin-1-yl,

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4-Benzoylpiperazin-1-yl, 4-(t-Butoxycarbonyl)piperazin-1-yl, Pyrrolidin-1-ylcarbonyl, Piperidin-1-ylcarbonyl, 3-Oxomorpholino, 3-Hydroxy-8-azabicyclo[3.2.1]oct-8-yl, 3-Acetyloxy-8-azabicyclo[3.2.1]oct-8-yl, 4-Fluorpiperidin-1-yl oder 4-Oxopiperidin-1-yl darstellt.

5 14. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^1 3,4-Dichlorphenyl darstellt.

15 15. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin R^2 4-Aminopiperidin-1-yl, 4-Carboxypiperidin-1-yl, 4-Hydroxypiperidin-1-yl, Morpholino, 1-Oxothiomorpholino, 4-Aminosulfonylpiperazin-1-yl, 4-Methansulfonylpiperazin-1-yl, 4-Dimethylaminosulfonylpiperazin-1-yl, 4-Morpholinosulfonylpiperazin-1-yl, 4-Piperidinosulfonylpiperazin-1-yl, 4-Fluorpiperidin-1-yl oder 4-Oxopiperidin-1-yl darstellt.

10 16. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin

15 (i) R Cyclohexylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 Morpholino darstellt;

(ii) R Cyclohexylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Aminosulfonylpiperazin-1-yl darstellt;

(iii) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Morpholinosulfonylpiperazin-1-yl darstellt;

20 (iv) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Aminosulfonylpiperazin-1-yl darstellt;

(v) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Dimethylaminosulfonylpiperazin-1-yl darstellt;

25 (vi) R Cyclopropylmethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Piperidinosulfonylpiperazin-1-yl darstellt;

(vii) R Cyclopropylethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 4-Aminosulfonylpiperazin-1-yl darstellt; oder

(viii) R Cyclopropylethyl darstellt, R^1 3,4-Dichlorphenyl darstellt, X Ethylen darstellt, X^1 eine direkte Bindung darstellt und R^2 Morpholino darstellt.

30 17. Verbindung oder Salz nach einem der vorangehenden Ansprüche, worin die Verbindung der Formel (I) die nachstehend in Formel (IA) an der Bindungsstelle der Gruppen X und R^1 am Glutarimidring gezeigte Stereochemie aufweist:

35

40

45

18. Pharmazeutische Zusammensetzung, umfassend eine Verbindung oder Salz nach einem der vorangehenden Ansprüche und ein pharmazeutisch verträgliches Verdünnungsmittel oder einen pharmazeutisch verträglichen Träger.

50 19. Verbindung oder Salz nach einem der Ansprüche 1 bis 17 oder Zusammensetzung davon nach Anspruch 18 zur Verwendung als ein Arzneimittel.

55 20. Verwendung einer Verbindung oder eines Salzes nach einem der Ansprüche 1 bis 17 oder Zusammensetzung davon nach Anspruch 18 zur Herstellung eines Arzneimittels zur Behandlung einer Erkrankung durch Erzeugen einer Antagonistenwirkung auf ein Tachykinin, das am Humanneurokinin-1-(NK₁)-, Humanneurokinin-2-(NK₂)- oder Humanneurokinin-3-(NK₃)-Rezeptor oder einer Kombination von zwei oder mehreren davon wirkt.

21. Verwendung nach Anspruch 20, wobei die Erkrankung eine entzündliche Erkrankung, wie Arthritis, Psoriasis, Asth-

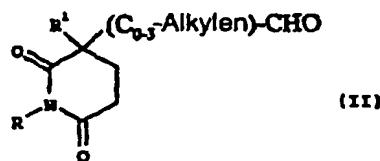
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ma oder entzündliche Darmerkrankung, eine Störung des zentralen Nervensystems (ZNS), wie Angstzustand, Depression, Demenz oder Psychose, eine Gastro-Intestinal-(GI)-Störung, wie funktionelle Darmkrankheit, reizbares Darmsyndrom, gastroesophagealen Reflux, Stuhlinkontinenz, Colitis oder Crohn'sche Krankheit, eine Urogenitaltraktstörung, wie Inkontinenz, Hyperreflexie oder Cystitis, eine pulmonale Störung, wie chronische obstruktive Luftwegserkrankung, eine Allergie, wie Ekzem, Kontaktdermatitis oder Schnupfen, eine Überempfindlichkeitsstörung, wie auf Giftsumach, eine periphere Neuropathie, wie diabetische Neuropathie, Neuralgie, Causalgia, schmerzvolle Neuropathie, Verbrennung, herpetische Neuralgie oder post-herpetische Neuralgie, Husten oder akuten oder chronischen Schmerz, darstellt.

10 22. Verbindung

(a) der Formel (II)

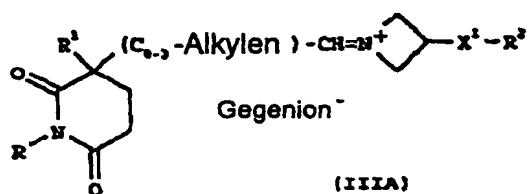
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worin R und R^1 wie vorstehend in Anspruch 1 definiert sind;
(b) der Formel (IIIA)

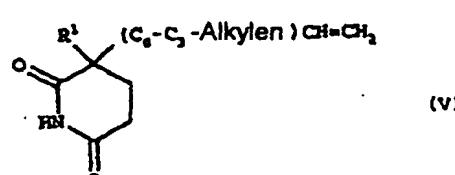
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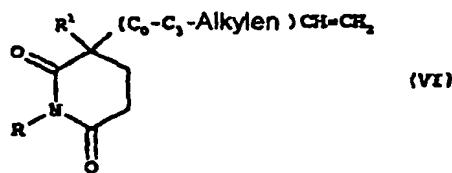
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35 worin R, R¹, X¹ und R² wie vorstehend in Anspruch 1 definiert sind, und das Gegenion Hydroxid oder Acetat darstellt;
 (c) Formel (V) oder (VI)

40



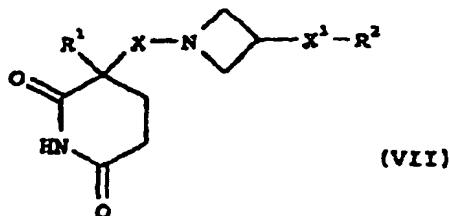
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worin R und R¹ wie vorstehend in Anspruch 1 definiert sind;
 (d) der Formel (VII)

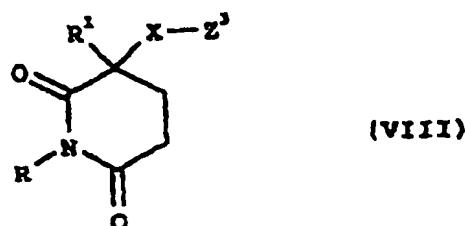
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15 worin X, X¹, R¹ und R² wie vorstehend in Anspruch 1 definiert sind;
 (e) der Formel (VIII)

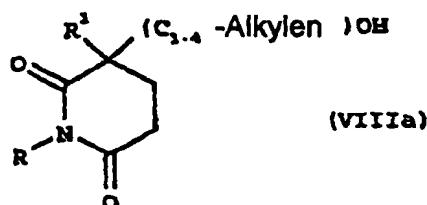
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30 worin X, R und R¹ wie vorstehend für eine Verbindung der Formel (I) definiert sind, und Z³ eine geeignete Abgangsgruppe, beispielsweise Chlor, Brom, Jod, Methansulfonyloxy, Trifluormethansulfonyloxy oder p-Toluolsulfonyloxy, darstellt;
 (f) der Formel (VIIIa)

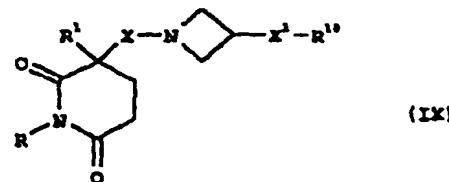
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45 worin R und R¹ wie in Anspruch 1 definiert sind;
 (g) eine Verbindung der Formel (IX)

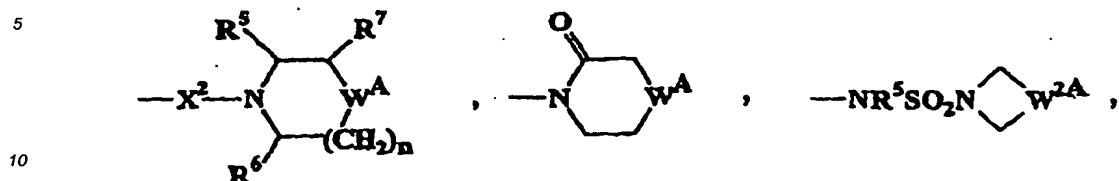
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worin R, R¹, X und X¹ wie in Anspruch 1 definiert sind und R¹⁰ eine Gruppe der Formel:

-NZ⁴R⁴, (C₃-C₇-Cycloalkyl-C₁-C₄-alkyl)Z⁴N-,



15



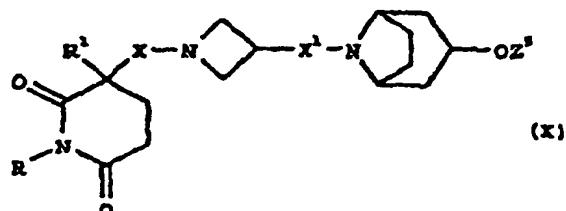
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darstellt, R^{9A}-NZ⁴R⁵ darstellt, W^A NZ⁴ oder CHNZ⁴R⁵ darstellt, W^{1A} CHNZ⁴R⁵ darstellt, W^{2A} W^{1A}, -CH₂W^{1A}-, -CH₂W^ACH₂- oder -CH₂CH₂W^ACH₂- darstellt, X, X¹, X², R, A, R¹, R⁴, R⁵, R⁶, R⁷, m und n wie vorstehend in Anspruch 1 definiert sind und Z⁴ eine geeignete Schutzgruppe, beispielsweise t-Butoxycarbonyl (z.B. eine Verbindung der Formel (I), worin W NCO₂C(CH₃)₃ darstellt oder R⁹-NR⁵CO₂C(CH₃)₃ darstellt), oder Benzylloxycarbonyl darstellt;

25

(h) der Formel (X)

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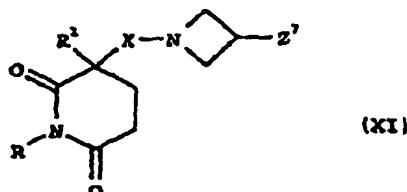
40

worin Z⁵ eine geeignete Schutzgruppe, beispielsweise Acetyl oder Tetrahydropyran-2-yl, darstellt, und X, X¹, R und R¹ wie vorstehend in Anspruch 1 definiert sind;

(i) eine Verbindung der Formel (XI)

45

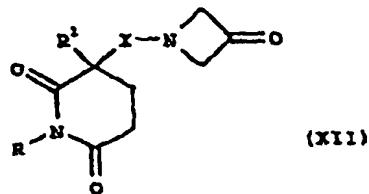
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55

worin x, R und R¹ wie vorstehend für eine Verbindung der Formel (I) definiert sind, und Z⁷ eine geeignete Abgangsgruppe, beispielsweise Methansulfonyloxy oder p-Toluolsulfonyloxy, darstellt;

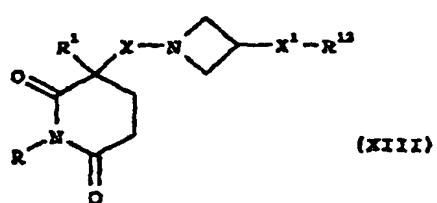
(j) der Formel (XII)



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worin X, R und R¹ wie vorstehend in Anspruch 1 definiert sind; oder
(k) der Formel (XIII):

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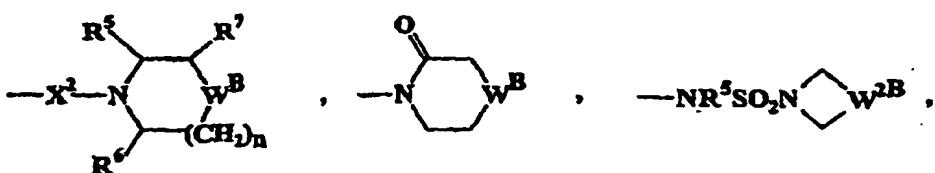


20

worin R¹²

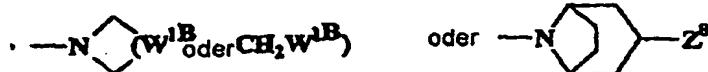
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darstellt,

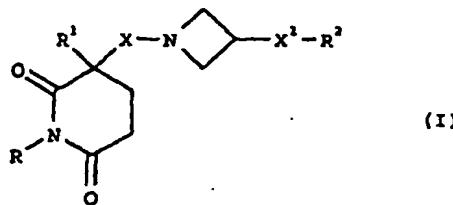
45 worin W⁸ und W¹B CHZ⁸ darstellen, W²B W¹B, -CH₂W¹B-, -CH₂W²BCH₂ oder -CH₂CH₂W²BCH₂- darstellt, Z⁸ eine geeignete Abgangsgruppe, beispielsweise Halogen, Methansulfonyloxy, Trifluormethansulfonyloxy oder p-Toluolsulfonyloxy, darstellt, und X, X¹, X², R, R¹, R⁵, R⁶, R⁷ und n wie vorstehend in Anspruch 1 definiert sind.

50

Revendications

1. Composé de formule (I) :

55



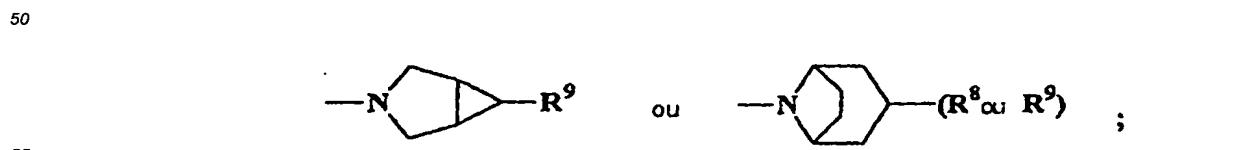
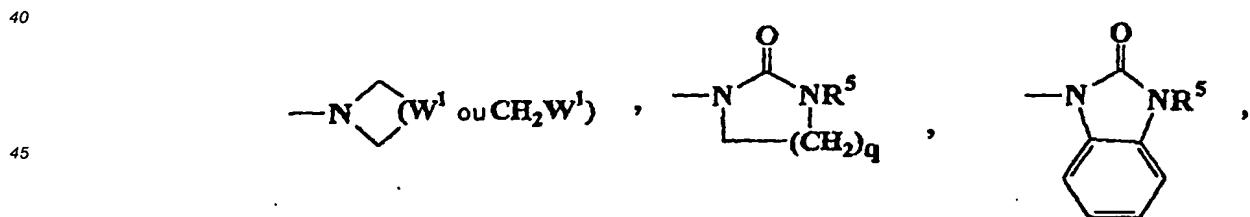
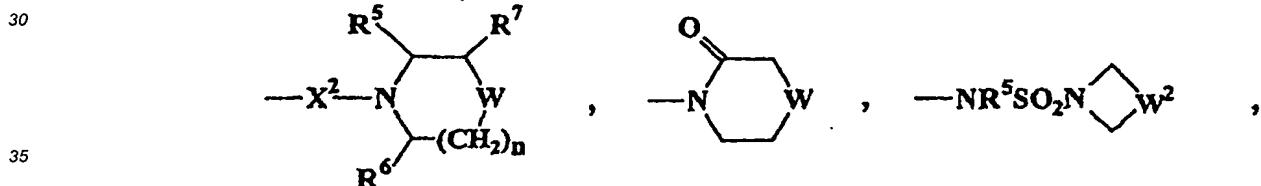
10

ou sel pharmaceutiquement acceptable d'un tel composé, dans lequel

15 R représente cycloalkyle en C₃-C₇, aryle ou alkyle en C₁-C₆, ledit groupe alkyle en C₁-C₆ étant facultativement substitué par fluoro, -COOH, -COO(alkyle en C₁-C₄), cycloalkyle en C₃-C₇, adamantyle, aryle ou het¹, et ledit groupe cycloalkyle en C₃-C₇ étant facultativement substitué par 1 ou 2 substituants dont chacun est indépendamment sélectionné entre alkyle en C₁-C₄, cycloalkyle en C₃-C₇, alcoxy en C₁-C₄, hydroxy, fluoro, fluoro(alkyle en C₁-C₄) et fluoro(alcoxy en C₁-C₄);

20 R¹ représente phényle, benzyle, naphtyle, thiényle, benzothiényle ou indolyle, dont chacun est facultativement substitué par 1 ou 2 substituants dont chacun est indépendamment sélectionné parmi alkyle en C₁-C₄, alcoxy en C₁-C₄, halogéno et trifluorométhyle;

25 R² représente -CO₂H, -CONR³R⁴, -CONR⁵(cycloalkyle en C₃-C₇), -NR⁵(alcanoyle en C₂-C₅), -NR³R⁴, -NR⁵CONR⁵R⁶, (cycloalkyle en C₃-C₇ - alkyle en C₁-C₄)R⁵N-, (cycloalkyle en C₃-C₇ - alkyle en C₁-C₄)₂N-, -NR⁵COCF₃, -NR⁵SO₂CF₃, -NR⁵(SO₂ alkyle en C₁-C₄), -NR⁵SO₂NR⁵R⁶, -NR⁵(SO₂ aryle), -N(aryl)(SO₂ alkyle en C₁-C₄), -OR⁵, -O(cycloalkyle en C₃-C₇), -SO₂NR⁵R⁶, het³ ou un groupe de formule :



R³ et R⁴ sont chacun indépendamment sélectionnés entre H et alkyle en C₁-C₄ facultativement substitué par

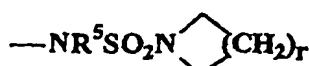
hydroxy, alcoxy en C₁-C₄, -S(O)_p(alkyle en C₁-C₄), amino, -NH(alkyle en C₁-C₄), -N(alkyle en C₁-C₄)₂ ou het² ;

5 R⁵ et R⁶ sont chacun indépendamment sélectionnés parmi H, alkyle en C₁-C₄ et cycloalkyle en C₃-C₇ - alkyle en C₁-C₄, lesdits groupes alkyle en C₁-C₄ et cycloalkyle en C₃-C₇ - alkyle en C₁-C₄ étant facultativement substitués par fluoro ;

R⁷ représente H, alkyle en C₁-C₄, hydroxy, fluoro(alkyle en C₁-C₄) ou phényle, ledit groupe phényle étant facultativement substitué par 1 ou 2 substituants dont chacun est indépendant sélectionné parmi alkyle en C₁-C₄, fluoro(alkyle en C₁-C₄), halogéno, alcoxy en C₁-C₄ et fluoro (alcoxy en C₁-C₄) ;

10 R⁸ représente H, fluoro, hydroxy, alcoxy en C₁-C₄, alcanoyle en C₂-C₅ ou alcanoxyloxy en C₂-C₅. R⁹ représente -NR⁵R⁶, -NR⁵COR⁵, -NR⁵SO₂CF₃, -NR⁵(SO₂) alkyle en C₁-C₄, -NR⁵SO₂NR⁵R⁶, -NR⁵COO(alkyle en C₁-C₄), -NR⁵CONR⁵R⁶, -NR⁵(SO₂ morpholino), -NR⁵(SO₂ aryle), -N(aryle) (SO₂ alkyle en C₁-C₄) ou un groupe de formule :

15



20 X représente alkylène en C₁-C₄ ;
 X¹ est une liaison directe ou un groupe alkylène en C₁-C₆ ;
 X² est une liaison directe, CO, SO₂ ou NR⁵CO où le groupe carbonyle est fixé à l'atome d'azote du cycle ;
 25 W représente méthylène, CO, CH(OH), C(OH)₂, CH(alcoxy en C₁-C₄), CHCO₂H, CHCO₂(alkyle en C₁-C₄), CHCONR⁵R⁶, CHF, CF₂, CH(azétidin-1-yle), CH(pyrrolidin-1-yle), CH(pipéridin-1-yle), CH(morpholino), CH(benzoxazol-2-yle), CHR⁹, O, S(O)_p, NR⁵, N(cycloalkyle en C₃-C₇), NSO₂(alkyle en C₁-C₄), NSO₂NR⁵R⁶, NSO₂CF₃, NSO₂(morpholino), NSO₂(aryle)

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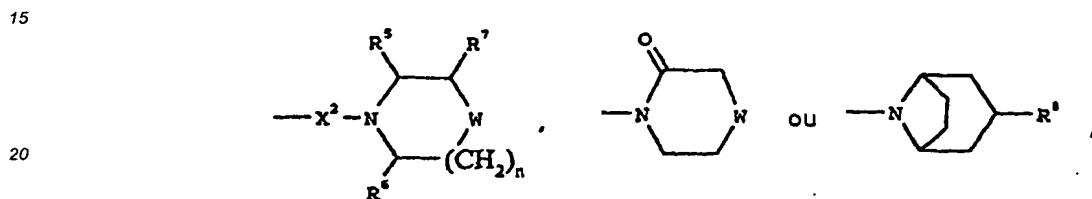


35 W¹ NCONR⁵R⁶, NCOR⁵, NCO(aryle) ou NCO₂(alkyle en C₁-C₄)
 représente méthylène, CO, CH(OH), C(OH)₂, CH(alcoxy en C₁-C₄), CHCO₂H, CHCO₂(alkyle en C₁-C₄), CHCONR⁵R⁶, CHF, CF₂, CH(azétidin-1-yle), CH(pyrrolidin-1-yle), CH(pipéridin-1-yle), CH(morpholino) ou CHR⁹ ;
 W² représente W¹, -CH₂W¹-, -CH₂WCH₂- ou -CH₂CH₂WCH₂ ;
 40 n représente 1 ou 2 lorsque W est autre que méthylène et représente 0, 1 ou 2 lorsque W représente méthylène ;
 p représente 0, 1 ou 2 ;
 q représente 1 ou 2 ;
 r représente 1, 2, 3 ou 4.
 45 "aryle", utilisé dans les définitions de R, R²-R⁹ et W, signifie naphtyle ou phényle, dont chacun est éventuellement substitué par alkyle en C₁-C₄, halogéno, -OR⁵, fluoro(alkyle en C₁-C₄), alcanoyle en C₂-C₅, -CONR⁵R⁶, -SO₂NR⁵R⁶ ou phényle ;
 "het¹", utilisé dans la définition de R, signifie thiényle ou un groupe hétéroaryle ayant un noyau à 5 ou 6 chaînons contenant soit 1 ou 2 atomes d'azote comme hétéroatomes, soit 1 atome d'azote comme hétéroatome et un atome d'oxygène ou de soufre comme hétéroatome, chacun étant facultativement substitué par 1 ou 2 substituants donc chacun est indépendamment sélectionné parmi alkyle en C₁-C₄, alcoxy en C₁-C₄, halogéno, fluoro(alkyle en C₁-C₄) et fluoro(alcoxy en C₁-C₄) ;
 50 "het²", utilisé dans les définitions de R³ et R⁴, signifie un groupe hétérocyclique non aromatique ayant un noyau à 4 à 7 chaînons contenant 1 ou 2 hétéroatomes dont chacun est indépendamment sélectionné entre l'azote, l'oxygène et S(O)_p, ledit groupe étant facultativement C-substitué par 1 ou 2 substituants dont chacun est indépendamment sélectionné parmi alkyle en C₁-C₄, alcoxy en C₁-C₄ et fluoro(alkyle en C₁-C₄), et ledit hétéroatome azote du cycle portant facultativement un substituant H, alkyle en C₁-C₄, alcanoyle en C₂-C₅, -CONR⁵R⁶ ou -SO₂NR⁵R⁶ ; et
 55 "het³", utilisé dans la définition de R², signifie un groupe hétéroaryle ayant un noyau à 5 chaînons facultati-

vement benzo-fusionné, lié par l'azote, contenant de 1 à 4 atomes d'azote comme hétéroatomes, lequel groupe het³ est facultativement substitué, y compris sur la partie benzo-fusionnée, par 1 ou 2 substituants dont chacun est indépendamment sélectionné parmi alkyle en C₁-C₄, fluoro et fluoro(alkyle en C₁-C₄).

5

2. Composé ou sel selon la revendication 1, dans lequel R représente aryle, cycloalkyle en C₃-C₇ facultativement substitué, ou un groupe alkyle en C₁-C₆ substitué par aryle ou cycloalkyle en C₃-C₇ facultativement substitué.
- 10 3. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R¹ représente phényle facultativement substitué par 1 ou 2 substituants halogéno.
4. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R² représente -CONR³R⁴, -CONR⁵ (cycloalkyle en C₃-C₇), -NR³R⁴, het³ ou un groupe de formule :



25 dans lesquels R³ et R⁴ sont chacun indépendamment sélectionnés entre alkyle en C₁-C₄ et alkyle en C₁-C₄ substitué par hydroxy ou alcoxy en C₁-C₄, R⁵ et R⁶ sont chacun indépendamment sélectionnés entre H, alkyle en C₁-C₄ facultativement substitué par fluoro et cycloalkyle en C₃-C₇ - alkyle en C₁-C₄, R⁷ représente H, hydroxy ou phényle, R⁸ représente hydroxy ou alcanoxy en C₂-C₅, W représente méthylène, CH(OH), CHF, CO, CH(alcoxy en C₁-C₄), CHCO₂H, CHCO₂(alkyle en C₁-C₄), CH(benzoxazol-2-yle), CHNR⁵R⁶, CHNR⁵COR⁵, CHNR⁵(SO₂ alkyle en C₁-C₄), CHNR⁵COO(alkyle en C₁-C₄), O, S(O)_p, NR⁵, NSO₂(alkyle en C₁-C₄), NSO₂NR⁵R⁶, NSO₂(morpholino), NSO₂(pipéridino), NCONR⁵R⁶, NCOR⁵, NCO(aryle) ou NCO₂(alkyle en C₁-C₄), n représente 1 ou 2 lorsque W est autre que méthylène et représente 0 ou 1 lorsque W représente méthylène, et p représente 0, 1 ou 2.

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35 5. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel X représente éthylène ou propylène.

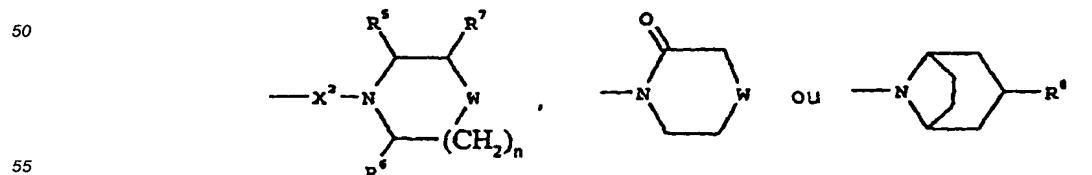
6. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel X¹ est une liaison directe.

7. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R représente cycloalkyle en C₃-C₇ facultativement substitué ou alkyle en C₁-C₆ substitué par cycloalkyle en C₃-C₇ facultativement substitué.

40 8. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R¹ représente phényle facultativement substitué par 1 ou 2 substituants dont chacun est indépendamment sélectionné entre fluoro et chloro.

9. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R² représente CONR³R⁴, CONR⁵(cycloalkyle en C₃-C₇), -NR³R⁴, un groupe hétéroaryle ayant un noyau à 5 chaînons lié via l'azote contenant 1 ou 2 atomes d'azote comme hétéroatomes, ou un groupe de formule

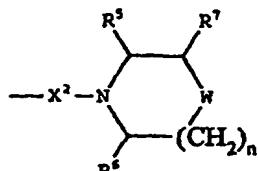
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où R³ et R⁴ sont chacun indépendamment sélectionnés entre méthyle et alkyle en C₁-C₄ substitué par hydroxy

ou méthoxy, R⁵ et R⁶ sont chacun indépendamment sélectionnés entre H, méthyle, trifluorométhyle et cyclopropylméthyle, R⁷ représente H, hydroxy ou phényle, R⁸ représente hydroxy ou acétyloxy, W représente méthylène, CH(OH), CHOCH₃, CHF, CO, CHOCH₂CH₃, CHO(CH₂)₂CH₃, CHOC(CH₃)₃, CHCO₂H, CHCO₂CH₃, CHCO₂CH₂CH₃, CH(benzoxazol-2-yle), CHNH₂, CHNHCH₂(cyclopropyle), CHNHCOCH₃, CHNHSO₂CH₃, CHNHCO₂C(CH₃)₃ O, S(O)_p, NH, NCH₃, NCH₂(cyclopropyle), NSO₂CH₃, NSO₂NH₂, NSO₂NHCH₃, NSO₂N(CH₃)₂, NSO₂(morpholino), NSO₂(pipéridino), NCONH₂, NCONHCH₃, NCOCH₃, NCOOCF₃, NCO(phényle) ou NCO₂C(CH₃)₃, n représente 1 ou 2 lorsque W est autre que méthylène et représente 0 ou 1 lorsque W représente méthylène, et p représente 0, 1 ou 2.

10 10. Composé ou sel selon la revendication 9, dans lequel R² est un groupe de formule :



dans laquelle R⁵, R⁶, R⁷ W et n sont tels que définis dans la revendication 9, et X² est une liaison directe.

25 11. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R représente 2-cyclopropyléthyle, cyclohexyle, 4,4-difluorocyclohexyle, cyclohexylméthyle ou cyclopropylméthyle.

12. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R¹ représente phényle, 3,4-difluorophényle, 3-chlorophényle, 4-chlorophényle ou 3,4-dichlorophényle.

30 13. Composé ou sel selon l'une quelconque des revendications 1 à 9 ou les revendications 11 ou 12, dans lequel R² représente
N-(2-méthoxyéthyl)-N-méthylcarbamoyle, N-cyclohexylcarbamoyle, N-(2-hydroxyéthyl)-N-méthylamino, N-(2-hydroxy-2-méthylpropyl)-N-méthylamino, N-(2-méthoxyéthyl)-N-méthylamino, imidazol-1-yle, 3-hydroxypyrrolidin-1-yle, pipéridin-1-yle, 2,6-diméthylpipéridin-1-yle, 3-hydroxypipéridin-1-yle, 4-hydroxypipéridin-1-yle, 4-méthoxy-pipéridin-1-yle, 4-éthoxypipéridin-1-yle, 4-(n-propoxy)pipéridin-1-yle, 4-(t-butoxy-pipéridin-1-yle), 4-carboxypipéridin-1-yle, 4-méthoxycarbonylpipéridin-1-yle, 4-éthoxycarbonylpipéridin-1-yle, 4-(benzoxazol-2-yl)pipéridin-1-yle, 4-aminopipéridin-1-yle, 4-cyclopropylméthylaminopipéridin-1-yle, 4-acétamidopipéridin-1-yle, 4-méthanesulfonamidopipéridin-1-yle, 4-(t-butoxycarbonylaminopipéridin-1-yle), morpholino, 2-phénylmorpholino, homomorpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, pipérazin-1-yle, 4-méthylpipérazin-1-yle, 4-cyclopropylméthylpipérazin-1-yle, 4-méthanesulfonylpipérazin-1-yle, 4-aminosulfonylpipérazin-1-yle, 4-méthylaminosulfonylpipérazin-1-yle, 4-diméthylaminosulfonylpipérazin-1-yle, 4-morpholinosulfonylpipérazin-1-yle, 4-pipéridinosulfonylpipérazin-1-yle, 4-carbamoylpipérazin-1-yle; 4-N-méthylcarbamoylpipérazin-1-yle, 4-acétylpipérazin-1-yle, 4-trifluoroacétylpipérazin-1-yle, 4-benzoylpipérazin-1-yle, 4-(t-butoxycarbonyl)pipérazin-1-yle, pyrrolidin-1-ylcarbonyle, pipéridin-1-ylcarbonyle, 3-oxomorpholino, 3-hydroxy-8-azabicyclo[3.2.1]oct-8-yle, 3-acétoxy-8-azabicyclo[3.2.1]oct-8-yle, 4-fluoropipéridin-1-yle ou 4-oxopipéridin-1-yle.

45 14. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R¹ représente 3,4-dichlorophényle.

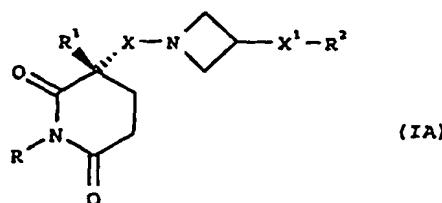
50 15. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel R² représente 4-aminopipéridin-1-yle, 4-carboxypipéridin-1-yle, 4-hydroxypipéridin-1-yle, morpholino, 1-oxothiomorpholino, 4-aminosulfonylpipérazin-1-yle, 4-méthanesulfonylpipérazin-1-yle, 4-diméthylaminosulfonylpipérazin-1-yle, 4-morpholinosulfonylpipérazin-1-yle, 4-pipéridinosulfonylpipérazin-1-yle, 4-carbamoylpipérazin-1-yle; 4-N-méthylcarbamoylpipérazin-1-yle, 4-acétylpipérazin-1-yle, 4-trifluoroacétylpipérazin-1-yle, 4-benzoylpipérazin-1-yle, 4-(t-butoxycarbonyl)pipérazin-1-yle, pyrrolidin-1-ylcarbonyle, pipéridin-1-ylcarbonyle, 3-oxomorpholino, 3-hydroxy-8-azabicyclo[3.2.1]oct-8-yle, 3-acétoxy-8-azabicyclo[3.2.1]oct-8-yle, 4-fluoropipéridin-1-yle ou 4-oxopipéridin-1-yle.

55 16. Composé ou sel selon l'une quelconque des revendications précédentes dans lequel
(i) R représente cyclohexylméthyle, R¹ représente 3,4-dichlorophényle, X représente éthylène, X¹ est une

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liaison directe et R² représente morpholino ;
 (ii) R représente cyclohexylméthyle, R¹ représente 3,4-dichlorophényle, X représente éthylène, X¹ est une liaison directe et R² représente 4-aminosulfonylpipérazin-1-yle ;
 (iii) R représente cyclopropylméthyle, R¹ représente 3,4-dichlorophényle, X représente éthylène, X¹ est une liaison directe et R² représente 4-morpholinosulfonylpipérazin-1-yle ;
 (iv) R représente cyclopropylméthyle, R¹ représente 3,4-dichlorophényle, X représente éthylène, X¹ est une liaison directe et R² représente 4-aminosulfonylpipérazin-1-yle ;
 (v) R représente cyclopropylméthyle, R¹ représente 3,4 dichlorophényle, X représente éthylène, X¹ est une liaison directe et R² représente 4-diméthylaminosulfonylpipérazin-1-yle ;
 (vi) R représente cyclopropylméthyle, R¹ représente 3,4-dichlorophényle, X représente éthylène, X¹ est une liaison directe et R² représente 4-pipéridinosulfonylpipérazin-1-yle ;
 (vii) R représente cyclopropyléthyle, R¹ représente 3,4-dichlorophényle, X représente éthylène, X¹ est une liaison directe et R² représente 4-aminosulfonylpipérazin-1-yle ; ou
 (viii) R représente cyclopropyléthyle, R¹ représente 3,4-dichlorophényle, X représente éthylène, X¹ est une liaison directe et R² représente morpholino.

17. Composé ou sel selon l'une quelconque des revendications précédentes, dans lequel le composé de formule (I) a la stéréochimie indiquée ci-dessous dans la formule (IA) au niveau de la position de fixation des groupes X et R¹ au cycle glutarimide :



18. Composition pharmaceutique comprenant un composé ou un sel selon l'une quelconque des revendications précédentes et un diluant ou un support pharmaceutiquement acceptable.

19. Composé ou sel selon l'une quelconque des revendications 1 à 17, ou composition d'un tel composé ou sel selon la revendication 18, pour une utilisation comme médicament.

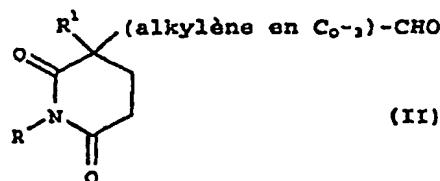
20. Utilisation d'un composé ou d'un sel selon l'une quelconque des revendications 1 à 17, ou d'une composition d'un tel composé ou sel selon la revendication 18, pour la fabrication d'un médicament pour le traitement d'une maladie par production d'un effet antagoniste à une tachykinine agissant au niveau du récepteur de la neurokinine-1 humaine (NK₁), neurokinine-2 humaine (NK₂), ou neurokinine-3 humaine (NK₃), ou une combinaison de deux de celles-ci ou davantage.

21. Utilisation selon la revendication 20, dans laquelle la maladie est une maladie inflammatoire telle que l'arthrite, le psoriasis, l'asthme ou la maladie inflammatoire de l'intestin, un désordre du système nerveux central (CNS) tel que l'anxiété, la dépression, la démence ou la psychose, un désordre gastro-intestinal (GI) tel qu'une maladie fonctionnelle de l'intestin, le syndrome d'intestin irritable, le reflux gastro-oesophagien, l'incontinence fécale, la colite ou la maladie de Crohn, un désordre de l'appareil uro-génital tel que l'incontinence, l'hyperréflexie ou la cystite, un désordre pulmonaire tel que la maladie d'obstruction chronique des voies respiratoires, une allergie telle que l'eczéma, la dermatite de contact ou la rhinite, un désordre d'hypersensibilité tel qu'au sumac vénéneux, une neuropathie périphérique telle qu'une neuropathie diabétique, une neuralgie, une causalgie, une neuropathie douloureuse, une brûlure, une neuralgie herpétique ou une neuralgie post-herpétique, la toux ou une douleur aiguë ou chronique.

22. Composé

(a) de formule (II)

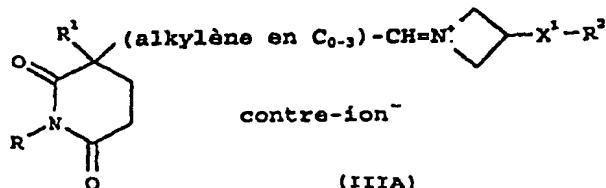
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dans laquelle R et R¹ sont tels que précédemment définis dans la revendication 1 ;
(b) de formule (IIIA)

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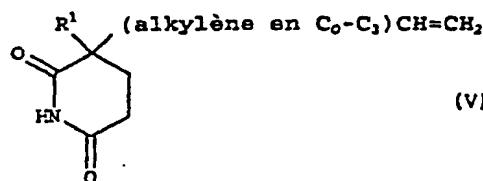


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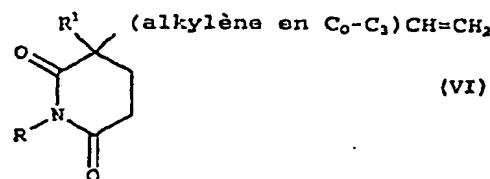
dans laquelle R, R¹, X¹ et R² sont tels que précédemment définis dans la revendication 1, et le contre-ion est un hydroxyde ou un acétate ;
(c) de formule (V) ou (VI)

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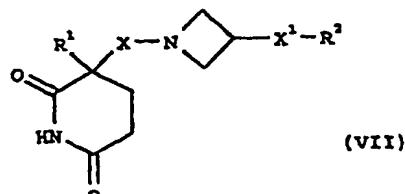
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dans laquelle R et R¹ sont tels que précédemment définis dans la revendication 1 ;
(d) de formule (VII)

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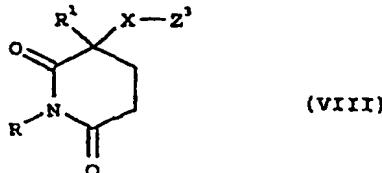


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dans laquelle X, X¹, R¹ et R² sont tels que précédemment définis dans la revendication 1 ;
(e) de formule (VIII)

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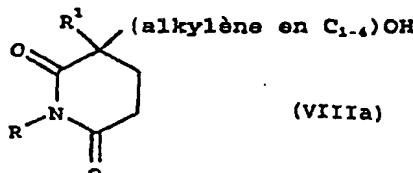
(VIII)

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dans laquelle X, R et R¹ sont tels que précédemment définis pour un composé de formule (I), et Z³ est un groupe labile convenable, par exemple chloro, bromo, iodo, méthanesulfonyloxy, trifluorométhanesulfonyloxy ou p-toluenesulfonyloxy ;
(f) de formule (VIIIa)

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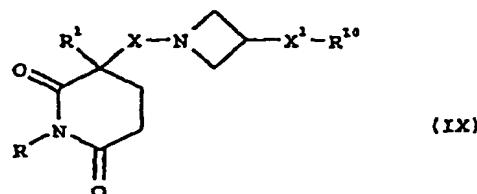
(VIIIa)

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dans laquelle R et R¹ sont tels que définis dans la revendication 1 ;
(g) d'un composé de formule (IX)

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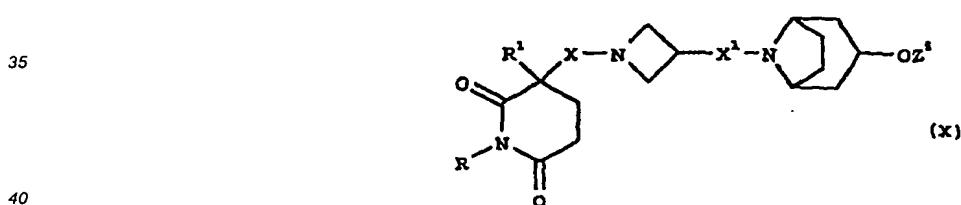
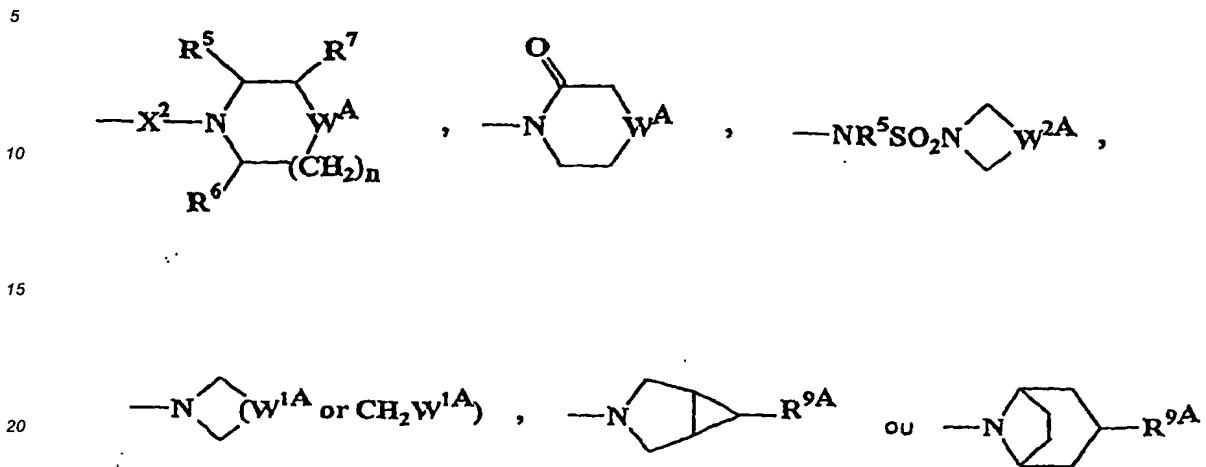


(IX)

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dans laquelle, respectivement, R, R¹, X et X¹ sont tels que définis dans la revendication 1 et R¹⁰ est un groupe de formule :

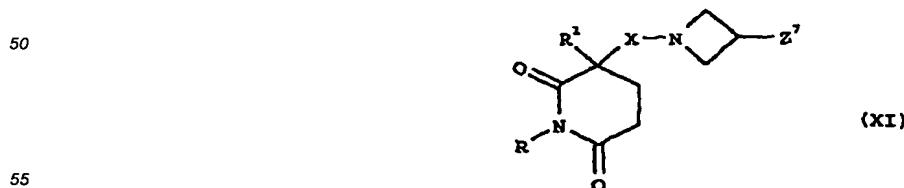
-NZ⁴R⁴, (cycloalkyle en C₃-C₇ - alkyle en C₁-C₄)Z⁴N-,



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dans laquelle Z⁵ est un groupe protecteur convenable, par exemple acétyle ou tétrahydropyran-2-yle, et X, X¹, R et R¹ sont tels que précédemment définis dans la revendication 1 ;

(i) d'un composé de formule (XI)

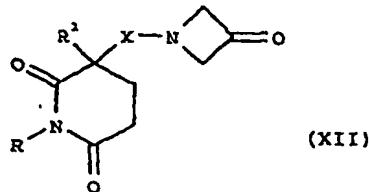


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dans laquelle X, R et R¹ sont tels que précédemment définis pour un composé de formule (I) et Z⁷ est un groupe labile convenable, par exemple méthanesulfonyloxy ou p-tolènesulfonyloxy ;
(j) de formule (XII)

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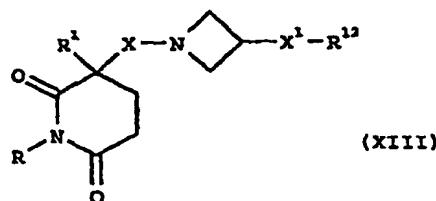


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dans laquelle X, R et R¹ sont tels que précédemment définis dans la revendication 1, ou
(k) de formule (XIII)

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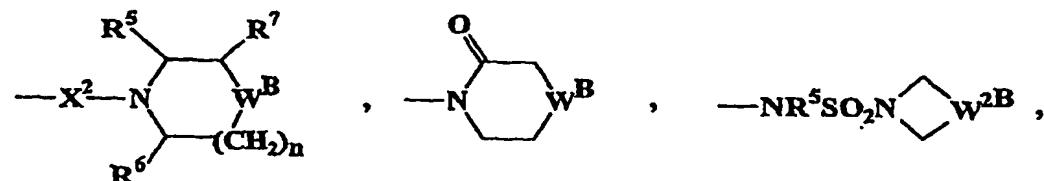
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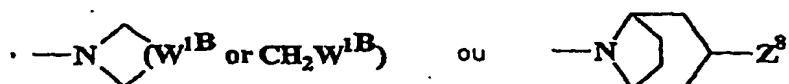
dans laquelle R¹² représente

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dans laquelle W^B et W^{1B} représentent CHZ⁸, W^{2B} représente W^{1B}, -CH₂W^{1B}-, -CH₂W^BCH₂- ou -CH₂CH₂W^BCH₂-; Z⁸ est un groupe labile convenable, par exemple halogéno, méthanesulfonyloxy, trifluorométhanesulfonyloxy ou p-tolènesulfonyloxy, et X, X¹, X², R, R¹, R⁵, R⁶, R⁷ et n sont tels que définis précédemment dans la revendication 1.

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